The problem of fertility control is of vital importance in view of the dangers of population explosion in our country. Attempts have been made in different laboratories to tackle this problem at the various steps in mammalian reproduction such as spermatogenesis, ovulation, fertilization, ovum transport in tube and uterus, blastocyst development and implantation. Pharmacological approach has been to intercept the fundamental mechanisms involved in each of above processes.

Hypothalamic control of production and release of gonadotrophins from the anterior pituitary is well established. It is recognised that reflex or neural influence reaching the appropriate hypothalamic nuclei releases an adrenergic transmitter probably dopamine at the level of median eminence which triggers the release of leutinising hormone releasing factor (L.H.R.F.). This in turn causes the release of leutinising hormone essential for the ejection of ova from the ovary. Reserpine and alpha methyl metatyrosine which deplete the catecholamine from the median eminence have been reported to cause significant prolongation of oestrus cycle in rats. Treatment of mice with adrenergic receptor blocking agents dihydroergotamine and dibenzyline have been reported to prolong the average duration of oestrus cycle (4). The use of the adrenergic blockades however could not be of practical utility because of their side effects. It may however be of interest that the sex hormones and particularly progesterone decrease dopamine significantly from the brain and progesterone derivatives have been successfully used for contraception.

Inhibition of ovulation during pregnancy was thought of as early 1898 by Beard (3), who suggested that corpus luteum might be involved in the suppression of the ovulation, and by 1937 it had become clear that the progesterone, testosterone and oestrogens could inhibit ovulation. These hormones however could not be put to practical use until 1954 when Djerassi and co-worker (8) demonstrated a new method of orally active progestogens following which a large number of 19 nortestosterone derivatives have appeared. Presently available oral contraceptives are combinations of synthetic oestrogens and progestogens which are given for 20 to 22 days beginning at 5th day of menstrual cycle with an object to inhibit ovulation and to provide a regular cyclic management. The contraceptive action

*Presented at the symposium held during XVII Annual Conference of the Association of Physiologists and Pharmacologists of India, Trivandrum, March 5-7, 1972.
of a combined regimen is also due to the alteration in the cervical mucous caused by progestrone being given from an early stage of the cycle.

In most preparations, the oestrogen component is either ethylestradiol as mestranol and progestrogens are either 19 nortestosterone or 17 hydroxy-progestrone. The oestrogen cause reduction in F. S. H. while progestrogens suppress the mid cycle peak of L.H., resulting in inhibition of ovulation. The progestin activity is also responsible for powerful haemostatic effects on the hormonal uterine bleeding. Long continued use of these steroidal agents is associated with menstrual changes, nausea, breast tenderness, weight gain, headache, vertigo and endometrial changes.

Post-coital non-steroidal contraceptives have been developed to affect the process of fertilization, implantation and development of ovum. These are the derivatives of aclylophenone, benzoferan, chroman, isoflavone naphthofuran, propiophenone and sulphones and have been found to be active to inhibit implantation (33). Of these 2-phenyl 3-p (B-pyrroldidine-ethoxy phenyl) 6-methoxy benzoferan (DBF) and phenyl naphthofuran (NF) were cent per cent effective contraceptives at the dose of 4 mg./kg. In mice DBF showed mild utrotrophic and anti-oestrogenic activity and interfered with delayed implantation tests (15). Single feeding of NF (10 mg/kg) prevented pregnancy in rhesus monkeys and other biological properties being similar to benzoferan. Anti-decidualogenic property has also been reported with this compound and the prevention of implantation has been attributed due to its anti-progesterone action which may be related to its intrinsic oestrogenic property whereas studies on DBF have shown that the anti-implantation activity is dependent upon the oestrogenicity. An anti-oestrogenic steroid 2-3 alpha epithic 17-B hydroxy 5-a andosterone as reported by Miyanke (25) produces implantation delay followed by fetal reabsorption when administered subcutaneously in period of pre-implantation.

Effects of intra-uterine contraceptive device (IUCD) have been studied by various workers (16, 6, 21) on the process ovulation, acceleration of passage of ova through the tube and implantation. The evidence to support any significant effect on ovulation or on ovum transport is meagre. Interference with implantation in presence of IUCD has however been substantiated by experimental data. The anti-implantation effects of loop have been investigated in consideration of changes in the endometrium, uterine fluid and hormonal effects etc. The uterine milieu is reduced by about 50% in volume in the presence of IUCD (15). Laumas and Yadav (22) have postulated that intra uterine contraceptive device IUCD produced estrogen like effects in rat uterus and the increased sensitivity of the uterus to progestrone at the time of implantation may produce asynchronous changes in the uterus to cause anti-implantation effects.

The presence of IUCD has also been found to cause accumulation of glycogen in the endometrium (27), mobilization of mast cells (23) and increase in total uterine content of histamine (26). Gulati and Gupta (9) while confirming the data on increase in the histamine content of the endometrium in IUCD bearing rats (2.12 ± 0.39) as compared to the control rats (2.05 ± 2.20).

More recently, the presence of IUCD does not affect ovulation and implantation in early mammalian albumin, uteroglobin and alpha-globulin (presumably protein) absorption sites.

One specific interest in the increased uterine protein absorption is the total protein content in the uterine fluid during the same period that is increased by 100% in the presence of IUCD. As the increased uterine fluid absorption is due to the anti-progesterone action, it is not surprising that the increased uterine fluid absorption is due to the anti-progesterone action (33).

Immunological to be involved in the immunological rejection of the implanted embryo and the site and timing of the rejection. The immunological rejection of the implanted embryo and the site and timing of the rejection are not fully understood.

Pregnant rabbit period of time that the immunological rejection of the implanted embryo and the site and timing of the rejection are not fully understood.

Kraicer and Lober (x 18) have characterized the anti-implantation effects of the uterine milieu. The anti-implantation effects of the uterine milieu are not fully understood.

Pregnant rabbit period of time that the immunological rejection of the implanted embryo and the site and timing of the rejection are not fully understood.
October 1972
Ind. J. Physiol. Pharmac.

the cervical mucous caused by ethylestradiol as mestranol and progestrone. The oestrogen mid cycle peak of L.H., also responsible for powerful continued use of these steroidal derness, weight gain, headache,

\[2\cdot \text{phenyl 3-(B-pyrroloffuran CNF)}\]

ice DBF showed mild utro'yed implantation tests Cl\(5\)).

onkeysand other biological property has also been reported attributed due to its antisiemens. Laumas(\(10\)) have also reported that the histamine content of endometrium during proliferative and secretory phases was markedly low (0.77 ± 0.47 and 1.12 ± 0.39) as compared to that observed in normal fertile women (4.5% ± 0.99 and 4.17 ± 2.20).

More recently, Kar et al (17) have also found changes in the uterine fluid of women bearing IUCD and Batta and Chaudhary (1) have demonstrated that the intra luminal fluid in presence of IUCD develops anti-implantation property. The role of uterine fluid protein a early mammalian development has been revived by Daniel (7). Uterine proteins include albumin, uteroglobin, transferrin, beta-globulin and gamma-globulin. Presence of histamine, a special alpha-globulin, collagen, acid muco-polysaccharides and at least 30 specific enzymes (presumably proteins) have been reported (9).

One specific uterine protein having a molecular weight 27000, called blastokinin is of special interest in that its concentration rises to reach relative proportion of almost 40% of the total protein content of uterus by 5th day and begins to recede by 6th day till it is almost absent on the 10th day. The changes run parallel with the changes in growth of blastocyst during the same period up to 8th day when implantation is proceeding and the embryo has ceased to be wholly dependent on uterine fluid. It is found to be a glycoprotein lacking gallic acid and containing few aromatic amino acids but more sulphur amino acids, and is identical to utero-globin. It stimulates mitosis in the dipausing blastocyst of mink, furseal in vitro, while in rabbit blastokinin accelerates the synthesis of RNA and protein in blastocyst. As the increased uridine uptake is directly reversible by Actinomycin-D and to a lesser degree by Puromycin, it is likely that blastokinin might be acting at the transcriptional level.

Immunological mechanisms similar to antigen and antibody type have been postulated to be involved in implantation of the mammalian egg by Tyler (32). Shelesnyak, Marcus, Kraicer and Lober (30) have also drawn attention to liberation of histamine at the implantation site and likened this to the inflammatory nature of a homograft rejection reaction. They consider that the antigens of the sperm sensitise the female so that she will react more strongly to the antigens expressed by the blastocyst when the zona pellucida is shed. There can be no doubt that at the time of implantation, the mouse blastocyst is antigenic. Kirby, Bollington and James (18) have shown that mouse blastocyst perish if transplanted to the kidney of specially immunised hosts.

Pregnant rabbit and probably the pregnant women will accept grafts for a longer period of time than will nonpregnant controls. Further when the uterus is decidualised, the immunological rejection of graft by the mother is prevented. Breyere et al, (4) have shown that following pregnancy, female mice will accept skin graft from the mating males strain for prolonged period of time indicating that transplantation antigen escape from the conceptus and that the mother recognises and respond to them. Heterogenous immune serum administered sub-cutaneously between mating and three days of pregnancy inhibited implantation
as the decidual reaction could not be induced by blastocyst. The sensitivity of uterus to a decidualizing stimulus could however be restored by daily treatment with progestrone. The blastocyst genetically dissimilar to the mother are more readily implanted than eggs which are genetically similar (19).

Recently Gupta and Gulati (10) have reported that the percentage release of histamine from the endometrium obtained from sterile women when incubated with chemical histamine releaser compound 48/80, dextran etc. was significantly less as compared to that released from the endometrium of normal fertile women. Similarly we have also observed difference in the ability of endometrium of sterile and fertile women with regard to uptake of histamine from male semen. Therefore, it seems that the sterility in such women may be related to non-reactivity of their endometrium.

The implanting blastocyst stimulates the endothelial mesenchymal cells to develop into decidual cells. The rate of trophoblast invasions is governed by the rate of decidual necrosis which starts near the site of implantation and spreads outwards to make rapid contact with the maternal blood supply to get nourishment. This invasion involves the dissolution of the surface of the endometrium by surface active proteolytic enzymes which provides site for fixation of blastocyst (19). Trypsin like activity in plasma has also been reported to increase during ovulation in certain species such as cockroaches (28). Whether such an increase in trypsin like activity occurs in women during ovulation is not known but some of the associated symptoms cold sweating similar to that occurring in pancreatitis may suggest enzyme activation (31). Further the active principals isolated from medicinal plants like Solanum nigrum Curcuma longa, Pisum sativum reported to have anti-implantation effects (5), have also been observed to inhibit trypsin and esterase activity in vitro test (11). It is therefore, likely that the anti-implantation effect of these drugs may be related to inhibition of trypsin.

Immunosuppressive agents, Prednisone and Prednisolone, have been commonly used steroids to suppress allograft regeneration effects. Similarly 6 mercaptopurines and aza-thiopurines effect the renal allograft rejection reactions and also influence the oval implantations if given before implantation has taken place. The experimental data on immunosuppressive agents though encouraging but it may not be of much therapeutic value for routine use due to their toxic effects on prolonged use.

Spermatogenesis in males has been selectively interrupted by steroids—the synthetic progestogens. A single injection of depot Progestogen (17 alpha-acetoxy 6 alpha methyl-pregn 4-ene-3, 20-dione) and (alpha ethyle 19 nor testosterone acetate-cyclopentyl enol) causes stimulation and reversible arrest of spermatogenesis in males without adverse effects (24). Antispermatogenetic effects of nitrofurones, nitropyrrols and dichloro-cyclyldiamines are dependent upon the availability of gonadotrophins. None of these substances appear to effect androgen production. On the other hand mesterolone, a steroid similar to testosterone has been reported to retain the peripheral attributes of androgens but
by blastocyst. The sensitivity of blastocyst was enhanced by daily treatment with

percentage release of histamine is compared to that released by untreated blastocyst. The sensitivity of blastocyst to histamine is more readily implanted by daily treatment with cortisone acetate, cyclopentyl enol) in males without adverse effects on spermatogenetic process in male. The experimental data though encouraging, the impairment of spermatogenetic process in male involves the dissolution of the ovum which provides site for the rate of decidual necrosis. The oval implantations if treated by steroids—the synthetic a-acetoxy 6 alpha methyl-D-nor progestesone a potent progestational hormone, is in developing a right attitude in thinking.

The pharmacological approach to intercept biochemical and physiological processes involved in mammalian reproduction has not only helped in the development of oral contraceptive agents, but has also helped in the unveiling of many mysterious and illunderstood steps of the reproductive biology. The efforts made in this direction have been encouraging and rewarding at least in developing a right attitude in thinking.

ACKNOWLEDGEMENTS

The author is thankful to the Director General, Indian Council of Medical Research, New Delhi for sponsoring the symposium and to the Association of Physiologists and Pharmacologists of India for giving him opportunity to participate in the symposium. He also thanks the Vice Chancellor Bhopal University for nominating him as delegate to the above Conference.

REFERENCES


