Physiologic Control of Fertility

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PHYSIOLOGIC CONTROL of fertility in higher forms, including man, is feasible for the following reasons:

1) In normal life there are alternate periods of fertility and infertility; neither ovulation nor spermatogenesis occurs before puberty, and, in the female, ovulation occurs only once during each menstrual cycle, is suspended entirely during pregnancy, and occurs only rarely during lactation.

2) During the reproductive period of life individuals may swing from normal germ cell production to aspermia or anovulation and then return to normal production again.

3) Fertility is not essential for physical well-being, inasmuch as many individuals have active and satisfying lives without producing sperm or ova.

4) The reproductive system (male and female regarded as one) is complex and delicately balanced.

5) Specific events must occur in the pituitary, in the ovary, in the testis, in the oviducts, in the uterus, and in the vagina in a well-ordered sequence if reproduction is to occur.

6) At each of these points there is a physicochemical system of checks and balances which operate in a specific relation to each other to make the critical steps possible.

7) A slight shift to the right or to the left of center—center being the limits of tolerance of agents or conditions which will permit the critical events to occur—is sufficient to prevent certain of the events and thus break the chain.

8) Shifts to the right or to the left can be caused by providing more of normally occurring substances, or by adding antagonists to neutralize them.

For the purposes of this discussion it will be assumed that reproduction begins with action in the anterior pituitary. This organ is responsive to nervous and hormonal stimuli and secretes, among other agents, gonadotropins, of which there are at least two: follicle-stimulating hormone (FSH), and luteinizing hormone (LH). FSH, in the female, stimulates follicle growth, and, in the male, spermatogenesis. LH stimulates ovulation. There is interdependence between FSH and LH, but the relationship is understood in general outline only. In the young adult female several hundred thousand ova are present in the ovaries. Early in the menstrual cycle FSH, arriving by way of the blood, stimulates follicle growth; this action is followed by release of one or more ova at a time near the middle of the menstrual cycle.

In the adult human male, sperm are formed continuously in the testis at a rate depending in part upon available gonadotropins. Mature sperm accumulate in the epididymis. Sperm are expelled along with fluids from the prostate and other glands upon ejaculation, at which time the sperm become motile. The condition of the seminal fluid is critical with respect to acidity, viscosity, nutrient content, enzymes, and hormones; and the fluid must be of such character as to activate the sperm and nourish them during passage to meet the ovum in the Fallopian tubes.

The ovum before fertilization is surrounded by a cluster of ovarian cells, the corona radiata, which may gather certain tissue cement during the early period in the tubes. It is believed by some that these surrounding materials must be dispersed by enzymatic action before sperm can penetrate and fertilization can be achieved.

The fertilized ovum is moved along the tube by ciliary action and by muscular contraction of the tubes. Rate of passage in the tubes is critical, inasmuch as development must have proceeded to the proper stage when the embryo arrives in the uterus. Furthermore, condition of the tubular fluid is critical. This fluid must be suitable not only for sperm nourishment and passage, but also for nourishment and passage of the fertilized ovum moving in the opposite direction.

Upon arrival in the uterus the developing organism must have reached the blastocyst stage. If the walls of the uterus have been properly conditioned, and a trophoblast formed, the trophoblast adheres to the uterine wall, and these two parts grow to form the placenta.

During the growth of follicles in the ovaries, certain of the follicular cells secrete estrogen. When an ovum erupts from the ovary, the follicle becomes modified to form the corpus luteum, which secretes progesterone.

Estrogen and progesterone are master hormones. They exert influence resulting in preparation for important steps in the reproductive cycle. Estrogens, in the main, induce those conditions which insure fertilization; among other effects, they cause the tubes to form fluids favorable for passage and nourishment of sperm and fertilized ova. Progesterone and related compounds, on the other hand, tend to insure implantation. Under the influence of progesterone (after action by estrogens) the uterus becomes conditioned to receive the developing embryo. The placenta, when formed, takes up secretion of progesterone—a function, which, as will be seen, has significance in the control of ovulation.

Of basic significance is the fact that both estrogens and progesterone suppress pituitary secretion of gonadotropins—estrogen suppressing secretion of FSH and progesterone suppressing secretion of LH. Early in the menstrual cycle, when estrogen output is low, pituitary secretion of FSH is free, and a new wave of follicles is stimulated to develop. As a consequence, estrogen output begins to rise, and this, in turn, stimulates the pituitary to release LH, which stimulates release of an ovum from one (or more) of the follicles more advanced in development. With quick development of the corpus luteum and release of progesterone, LH is suppressed, and, as a consequence, no other ovulations occur during that particular cycle and partially developed follicles undergo atresia. As the result of both estrogen and progesterone secretion, changes occur in the uterus consisting of endometrial proliferation and glandular growth. If fertilization does not occur, this growth of tissues is unnecessary, and the endometrial layers are sloughed off at the time of the menstrual period. This cycle of events—consisting of the estrogenic and progestational phases—requires a period of approximately 28 days.

Of interest is the fact that ovulation sometimes fails to occur in some individuals during the 28-day cycle, and, in some, ovulation fails to take place at all. These conditions sometimes can be corrected by regulating hormone balance. Such facts justify the point of view that reproduction is dependent on a delicate system of checks and balances, and that a slight shift to the right or left at a critical time at certain locations will prevent reproduction without impairment to health, sexual vigor, or subsequent reproduction.

Two other points are of interest. The first, already mentioned, is that ovulation does not occur during pregnancy, because progesterone is secreted continuously by the placenta during pregnancy. The second is that in certain animals pseudo-pregnancy may occur as a result of sterile matings; the female in such cases experiences a period during which no ovulation occurs and several cycles are missed. This gives additional support to the view that ovulation can be controlled by shifts in the hormone balance.

Turning again to the male, it is known that a shift in the hormone balance will reduce or stop spermatogenesis entirely for limited periods of time, depending on the type and duration of treatment.

Control Approaches

During the past three decades, and particularly during the past few years, many papers have been published giving leads as to how fertility can be influenced or controlled by modification of conditions at one or another of the critical points. Some of the studies have been concerned specifically with the problem of control of fertility, but the majority have been devoted to other problems such as sterility, nutrition, immunology, cancer, and animal husbandry. We are aware of only three other attempts to bring together literature on this subject (*1–3*).

Agents or approaches for physiologic control of fertility may be grouped under general headings as follows: hormones, anti-hormones, anti-enzymes, immune bodies, modified media, symbiotic organisms, dietary factors, special agents, nervous stimuli, and rhythm (detection of ovulation). These topics will be considered in order, but it should be borne in mind that the listing of references in each case is representative rather than exhaustive.

I. *Hormones*:

General Developments. Evidence that fertility can be controlled by administration of hormonal agents became available as early as 1921, when Haberlandt (*4*) showed that the transplantation of ovaries from pregnant laboratory animals into mature females of the same species caused the latter to be sterile for limited periods. Haberlandt ascribed the result to the presence of corpus luteum hormone in the transplanted ovaries. Later Scaglione (*5*) observed that temporary sterility in female laboratory animals is produced by implantation of male gonads and by injection of testicular extracts. Parkes and Bellerby (*6*) injected corpus luteum extract into mice and rats and observed inhibition of ovulation and estrus for prolonged periods.

As early as 1937 Kurzrok (*7, 8*) set forth a clear prospectus for temporary hormonal sterilization. This author called attention to the fact that women in good health sometimes have sterile menstrual cycles—that is, cycles in which ovulation does not occur. Kurzrok pointed out that, when ovulation is absent, the corpus luteum fails to form and the endometrium retains its post-menstrual characteristics, but that bleeding occurs cyclically about every four weeks. He noted that anovulatory cycles are typical during lactation and stressed that the anovulatory cycle is one method by which the organism limits its own fertility. Novak (*9*) gave further recognition to the significance of anovulatory cycles in women.

Additional strength was given to the idea of hormonal control in 1927 when Frank (*10*) and Davis and Koff (*11*) showed that intravenous injection of pregnant mare's serum into anovulatory women would result in ovulation, fertilization, and pregnancy.

Editorials by Abraham Stone in the *Journal of Contraception* (*12*) and in *Human Fertility* (*13*) also set forth a picture of hormonal control of fertility.

Sturgis (*14*) reported a study of estrogen therapy for dysmenorrhea. On the assumption that dysmenorrhea is associated with ovulation and that ovulation can be prevented by administration of estrogen, the following information was found significant in relation to the problem of fertility control. If the first of a series of 6 to 12 injections was given within the first week after onset of the menses, the next period would invariably be free from uterine cramps, whereas, if the series was not started until two weeks after onset, there was no alleviation at the time of the subsequent bleeding. These observations gave credence to the view that follicle growth can be suppressed by the administration of estrogens.

A study by Cole (*15*) was devoted to appraisal of the general principle of hormone regulation in the body and is typical of many since the concept of hormone control was first set forth. Cole brings together from various sources evidence showing that estrogens, progesterone, and androgens act to inhibit pituitary secretion of gonadotropins, thereby inhibiting follicular growth, ovulation, or spermatogenesis.

Sturgis (*16*), referring to the work of others, calls attention to the fact that there are around 400,000 ova in the ovaries of a young adult woman and that they undergo changes and disappear during the reproductive life. He also pointed out that, in the human cycle, usually only one egg escapes from the ovaries during each month, and that, since the reproductive span of a woman's life runs approximately from the twelfth to the fiftieth year, not more than 500 are released by one woman for potential fertilization and the others disappear by atresia. The picture developed by Sturgis stresses that, in the procession of developing follicles, there are first-rank follicles which mature and release ova, and second-rank follicles which undergo some development and then degenerate.

Evans *et al.* (*17*) demonstrated that purified lactogenic hormone will induce functional activity of corpora lutea. Since corpora lutea secrete progesterone, which in turn inhibits pituitary release of LH, it is clear why ovulation rarely occurs during lactation. Three articles by Byrnes and Meyer (*18–20*) indicate that in certain respects the effects of estrogen and progesterone are additive in inhibiting gonadotropic hormone secretion by the pituitary, and that the amounts of these agents required are small and within "physiologic" limits. These authors showed also that proportionately more estrogen is required to decrease FSH and to stimulate LH in the adolescent than in the adult and, on the basis of this observation, suggested that higher levels of FSH are an important factor in the attainment of sexual maturity.

Estrogens Alone. As early as 1932 Moore and Price (*21*) administered estrogen continuously to rats over a period of time and demonstrated that the gonadotropic potency of the pituitary is decreased. In the same year Meyer *et al.* (*22*) obtained similar results, also in rats. In 1937 Burdick and Whitney (*23*) injected 100 to 500 rat units of the estrogen progynon-B, causing acceleration of the rate of passage of ova through the Fallopian tubes of mice and a consequent condition of infertility. Whitney and Burdick (*24*) found that single injections of 5000 rat units of this estrogen given after ovulation result in accelerated tubal passage of the fertilized ova in rabbits, and that the developing ovum in the early cleavage stages disintegrates within a few hours after exposure to the uterine fluids; furthermore, they showed (*25*) that 100 to 500 rat units of progynon-B given to mice resulted in degeneration of the fertilized ova, the degeneration appearing to result from lack of proper sustaining fluid in the uterus, and not from the agent.

Parkes *et al.* (*26*) showed that small doses of ethinylestradiol or diethylstilbestrol administered by mouth prevent implantation of the blastocyst in the rabbit if given soon after ovulation, or they may terminate pregnancy. The effect of the agents, it is said, is produced in essentially a physiological manner; the luteal phase of the cycle is suppressed and another phase is induced, which, though not abnormal in itself, is unsuitable for development of the embryo. These authors state that everything we know about the menstrual cycle of primates suggests that its hormonal control is the same as in lower animals, and it is extremely probable that the factors governing implantation of the fertilized egg are fundamentally similar in women and in lower animals.

Hamblen *et al.* (*27*) administered diethylstilbestrol to women, giving doses of 2–6 mg per day on the fifth to the fourteenth or the twenty-fourth days of the menstrual cycle and observed marked variations in the length and duration of cycles and in amount of bleeding. These workers stated that the alterations were due in part to suppression of ovulation. Thompson (*28*) presented evidence showing that menstrual blood and dead endometrial cells contain a factor which stimulates pituitary release of FSH. Finnerty and Meyer (*29*) studied the effects of estrogen upon pituitary cytology and function and found a reduction in the gonadotropic content of the pituitary. They also found that the percentage of basophile cells in the pituitary was decreased in direct proportion to the concentration of estrogen administered. This, they pointed out, is evidence that the basophile cells of the pituitary are responsible for secretion of gonadotropins. The general picture is developed still further by Paschkis and Rakoff (*30*) in a study of the physiology of estrogenic hormones.

Progesterone Alone. Haberlandt (*31*) administered corpus luteum extracts intramuscularly or orally to laboratory animals and observed temporary sterility. Dempsey (*32*), in a study of reproductive activity in the guinea pig, showed that such widely differing experimental procedures as pregnancy, removal of corpora lutea, injection of progesterone, estrogen, testosterone, or androsterone benzoate do not influence the basic growth of follicles during the reproductive cycle, but that follicle growth is abolished completely by hypophysectomy; he concluded that progesterone inhibits pituitary release of LH.

Makepeace *et al.* (*33*) studied the effect of progestin and progesterone on ovulation in the rabbit and found that progesterone inhibited pituitary release of LH. Likewise, Astwood and Fevold (*34*) investigated the effect of progesterone on gonadotropic activity of the pituitary in rats and observed that this agent inhibited the release of LH.

Burdick (*35*) investigated the effect of progesterone on ovaries and embryos of mice and determined that daily injections of 1 mg of this agent to female mice, starting on the day of mating, prevented implantation but that implantation was not prevented when the treatments were started one day later. This worker observed that embryos continued to grow during treatment but died within a few days after treatment was stopped. Corpora lutea were found to undergo regression during treatment.

Boyarsky *et al.* (*36*) administered progesterone to estrual rabbits for 10 days before experimental ovulation and observed a marked suppression of fertilization. Dutt and Casida (*37*) gave 5–10 mg of crystalline progesterone daily to ewes during the active mating season and found ovulation inhibited during the treatment period in all animals maintained on the larger dosages but in only part of those maintained on the smaller dosages. It was found, however, that estrus occurred in all animals 3 to 5 days after termination of treatment.

Ulberg *et al.* (*38*) studied the ovarian response in heifers to progesterone injections. They gave 50 mg daily and found that heat and ovulation were prevented if the treatments were started before heat occurred. Similar studies were carried out by Ulberg *et al.* (*39*) on gilts: 12.5, 25, 50, and 100 mg of progesterone per day were injected, and it was found that the larger doses inhibited heat and ovulation during the treatment period when injections were started early enough in the estrous cycle. Bradbury (*40*) administered 5-, 50-, and 100-mg doses of progesterone per day to human females and found that 20 mg per day for one week was usually sufficient to prevent menstruation.

Estrogen and Progesterone. Musser (*41*) stated that dysmenorrhea can be prevented in any cycle by preventing ovulation and that the administration of large daily doses of estrogen, beginning 4 days after the start of menstruation, will prevent ovulation. This author goes on to suggest that 1 mg of diethylstilbestrol could be given orally, beginning the first day of menstruation, in such a way as to have a fertility control effect, and that progesterone could be given to bring about menstruation.

Long and Bradbury (*42*) gave daily doses of 25 mg of progesterone plus 2.5 mg of estrogen to women and found a delay of menstruation of 3 to 6 weeks which was accompanied by decidual changes induced in the endometrium. Doses of 10 mg of progesterone plus 1 mg of estrogen, 25 mg of progesterone alone, or 2–5 mg of estrogen alone did not have these effects.

Androgen Alone. Burdick *et al.* (*43*) administered large doses of testosterone propionate to female mice and observed rapid passage of ova through the oviducts followed by failure of implantation.

Ludwig (*44*) showed that low doses of testosterone propionate suppressed pituitary secretion of gonadotropins, with consequent loss of sperm formation in laboratory animals, and that high doses, while they likewise inhibited the pituitary, resulted in a level of androgen which stimulates the seminiferous tubules directly.

Heckel *et al.* (*45, 46*) administered testosterone propionate (50 mg three times per week) to men and observed a fall in sperm count which approached zero level in a matter of days and which was maintained as long as the treatment was continued. In the work described the aspermic conditions were maintained as long as 3 months or more. After cessation of treatment recovery of sperm production occurred rapidly and sometimes reached levels higher than previously existed ("rebound" phenomena).

These observations add strength to the view that testosterone and estrogen produce effects in the male or in the female which are similar, and also to the view that rate of passage of developing ova through the oviducts is critical.

Other Agents — Prolactin, Hormone-Metabolites. Dresel (*47*) administered prolactin to mature nonparous mice and found the estrous cycle to be suspended for about 3 weeks. Similarly Lahr and Riddle (*48*) showed temporary suppression of ovarian cycles in rats and mice with prolactin.

Hisaw and Velardo (*49*) studied the action of pregnanediol (non-estrogenic fraction), which is one of the end products of progesterone metabolism, and found, in case of the decidual reaction in rats, that the agent was antagonistic to progesterone. This agent is of interest inasmuch as it is an end product of progesterone metabolism and accordingly would not be expected to exert the multiplicity of physiological effects that would be exerted by progesterone or by estrogen. Being an antagonist of progesterone, it may be expected to interrupt fertility by prevention of endometrial growth and perhaps by other means.

II. *Anti-hormones*:

Gonadotropins are protein in character and accordingly may be expected to induce antibody formation when used as antigens. Parkes and Rowlands (*50*) studied the inhibition of ovulation in the rabbit, using anti-gonadotropic serum. They found that such serum, obtained by prolonged injection of rabbits with ox anterior pituitary extract, inhibited the ovulation-producing activity of the antigenic extract itself. When the serum was administered intravenously to rabbits immediately after mating, ovulation, which ordinarily would have occurred in 10 to 12 hours, did not occur.

Gegerson (*51*) made similar studies in rabbits and obtained positive precipitin reactions. These authors were inclined, however, to believe that the inhibiting substance was separate and distinct from the antiprotein substances obtained. Thompson (*52*) presents an even more extended study and review.

Deutsch *et al.* (*53*) determined the time of appearance of the properties of anti-gonadotropic and progonadotropic substances of rat serum. Sera were obtained which had pro- and anti-gonadotropic effects in rabbits that had been injected with sheep pituitary extracts over prolonged and varying periods of time.

Jungck and Brown (*54*) administered gonadotropins to anovulatory females, with the hope of stimulating ovulation. The gonadotropins used were of animal origin, and the patients soon developed an immunity reaction to the agents being used, with the consequence that the agents were relatively ineffective in inducing ovulation.

III. *Anti-enzymes*:

In 1950 Meyer and McShan (*55*) made an extensive study (157 references) of hormone-enzyme relationships. They pointed out that changes in concentration of enzymes occur in tissues and organs under the influence of hormones, and that the enzyme value of organs and organelles should be interpreted in terms of enzyme levels in those organelles.

Many enzymes are involved in the reproductive process, but, so far as is known, attempts to develop an anti-enzyme which would break a link in the reproductive chain have been carried out in relation to only one enzyme—hyaluronidase, which is present at higher levels in semen.

McLean and Rowlands (*56*) demonstrated that bull testis hyaluronidase causes dispersion of the coronal cells surrounding recently ovulated mammalian ova. Fekete and Duran-Reynals (*57*) extended the study, pointing out that crude or highly purified preparations, known to be rich in hyaluronidase (extracts from rattlesnake venom, leech tissues, and testicles), have a very pronounced effect in dispersing the follicular cells surrounding the ova of mice. Later, Leonard and Kurzrok (*58*) demonstrated dispersion of coronal cells surrounding recently ovulated mammalian ova with bull testis hyaluronidase. Four papers (*59–62*) indicate that normal human seminal fluid contains higher levels of hyaluronidase. Six other papers (*63–68*) show that hyaluronidase content of semen is roughly proportional to the sperm count. Greenberg and Gargill (*69*) and Chang (*70*) raise questions about whether hyaluronidase is carried exclusively by the sperm, pointing out the possibility that seminal fluid may carry this substance. Kurzrok (*67*) stressed that the motility of sperm is in no way related to their hyaluronidase content. Kurzrok attempted to utilize hyaluronidase to overcome sterility in human males but without significant success.

Perlman *et al.* (*71*) were able to demonstrate that the level of hyaluronidase in the medium surrounding rat testis suspensions was increased by subjecting the cells to adverse treatments, such as freezing, incubation, and toluene. Pincus *et al.* (*72*) showed that hyaluronidase inhibitors may be used in rabbits to prevent the follicle cell dispersing activity of sperm hyaluronidase, thereby preventing fertilization.

Chang (*73*) raised an additional question about the actual importance of hyaluronidase *in vivo,* since in the clinical studies application of hyaluronidase in human infertility gave generally negative results.

Martin and Beiler (*74*) used phosphorylated hesperidin, a hyaluronidase inhibitor (20 mg/kg when given intraperitoneally, or 100 mg/kg when given orally) and found litter size and number of litters in rats markedly reduced.

Of particular interest is the fact that Sieve (*75*) has used phosphorylated hesperidin in human beings (300 couples) for the specific purpose of fertility control, and he reports clear-cut, positive results. Three times daily 100–200 mg of phosphorylated hesperidin in tablet form was given orally to both males and females. Ten days were allowed for the substance to reach saturation in both the man and the woman, after which no other contraceptive protection was utilized. The period of protection among the 300 couples varied from 3 to 30 months, and 220 couples bore normal offspring after termination of use of the agent. Only two couples developed pregnancies during the periods of intended protection, and each of these admitted negligence in maintaining saturation of the agent.

IV. *Immune Bodies*:

Attempts have been made to employ the principles of both passive and active immunity in the control of fertility.

Passive Immunity. The information available is given under anti-hormones above. It is evident that immune bodies can be developed which act antagonistically to gonadotropins, but, since constant application would be required to counteract continuous secretion of gonadotropins by the pituitary, it is doubtful that this approach will be significant from a practical point of view.

Active Immunity. Spermatotoxins: Many workers have held the view that immune bodies could be produced in the female of a given species by using sperm from the same or other species as an antigen to cause sperm to become ineffective upon deposit in the female.

The most direct work thus far performed for physiologic control of fertility has utilized the principle of active immunity. Our bibliography contains sixteen references indicating positive findings of one kind or another (*76–91*). About half of these deal with studies in human beings. More recently Henle and co-workers (*92–95*), and Parsons and Hyde (*96*), using pure strain animals and carefully devised immunological techniques, have obtained negative results, thus raising the question of the reliability of previous findings. Of interest would be work with males to reduce the effectiveness of sperm.

Wharton's Jelly. Langer (*97, 98*) utilized crude extracts of Wharton's Jelly as an antigen, attempting to produce immune bodies in female rats and mice against the formation of embryonic tissues, and found a significant reduction in number of litters and litter size.

V. *Modified Media*:

Cervical Mucus. The fluid content of the uterus is complex, and its requirements for reproduction are specific within narrow limits. It must be favorable for the transport of sperm and also for support and maintenance of the blastocyst for a limited period. Cervical mucus is made up of secretions from the cervical glands, contributions from the oviduct, and probably also from materials drawn up from the vagina at the time of coitus. The mucus is comprised of a vast array of substrate materials, enzymes, hormones, steroids, and other special agents. Concentration, viscosity, and acidity are critical. The complexity of cervical mucus and the need for information with respect to the physiology of the uterus have been indicated by several authors (*99–109*).

Pommerenke observed that, at mid-cycle in human beings, the cervical mucus is increased in amount, acellularity, water content, and fluidity, and that, at this time, it is well supplied with carbohydrates and, presumably, amino acids. Pommerenke emphasizes that, because of these conditions, the sperm, on deposit in the vagina, must find an environment propitious for their nutrition and migration through the cervical canal. As has been pointed out above, these conditions are the consequence of estrogenic action. This author studied the effects of various hormones on recently castrated women. An estrogen product was found to stimulate cervical mucus secretion, which occurs at mid-cycle in normal subjects, whereas progesterone had no effect. The studies of Hughes (*103, 104*) furnish evidence that spontaneous abortion in human females can often be traced to a poorly functioning endometrium. His studies also show that, by means of therapeutic procedures designed to improve the functional qualities of the endometrium, women with a previous history of several abortions can achieve successful deliveries. Although the potentialities for control of fertility by modification of the cervical mucus are very great, no *in vivo* attempts have been made, so far as is known, to modify this complex physiology to reduce the probability of fertility.

Tubular Fluids. Much of what has been said about the physiologic complexity of the cervical mucus is also true of the tubular fluids. Burdick *et al.* (*110*) have shown that, if the tubes are distended by hormone stimulation so that the ovum cannot move at the appropriate rate, aging proceeds too rapidly in relation to the progress made and as a consequence implantation does not occur.

Semen. The physiologic condition of semen is similar to that of the cervical mucus and the fluid of the tubes. Concentration of substrate materials, pH, viscosity, enzymes, and hormone content are important, and the conditions of all must be maintained within narrow limits. Mann (*111–113*) has carried out extensive studies on metabolism of semen. He gives 336 references (*114*).

Bishop and Mathews (*115*) have shown an interesting inhibition of sperm motility by tetrazolium salts. They state that it is justifiable to conclude that the tetrazolium effect on sperm motility is not merely a reduction accompanying dehydrogenase activity, but is a physiological inhibition of a different order.

VI. *Symbiotic Organisms*:

Carter and Jones (*116*) and Matthews and Buxton (*117*) have made studies of the bacterial flora in the vagina and uterus of the human female. Their evidence indicates that some of the organisms must be responsible for infertility, inasmuch as treatment with antibiotics and elimination of certain of the species result in pregnancy. These observations suggest the possibility of organisms which can be transmitted from one individual to another for the purpose of preventing conception. The problem then would be merely one of elimination of the organisms by antibiotics for periods when conception is desired. Techniques are already known for accomplishment of this result.

VII. *Dietary Factors*:

Much evidence indicates that reproduction is affected by the presence or absence of specific factors in the diet. The seat of action, however, is often difficult to identify, because the presence or absence of dietary elements may cause modifications at several points.

With respect to inanition, Mason (*118*) and Ball *et al.* (*119*) studied the effects of starvation in rats and mice, respectively, and Smith (*120, 121*) observed the effects on human beings in Holland during World War II. In all three studies fertility was reduced, but the reduction was apparently due to simple lack of nourishment throughout the entire body.

In 1927 Evans and Burr (*122*) demonstrated that successful reproduction is dependent upon the fat-soluble vitamin E. Barrie (*123*) administered vitamin-E-deficient diets to rats and observed interruption of gestation. Evans (*124*) and Mason (*125*) observed fetal death, prolonged gestation, and difficult parturition in the rat as a result of vitamin A deficiency.

Holt *et al.* (*126*) maintained three male subjects on a diet deficient in arginine for 10 days. On the ninth day the seminal plasma of these subjects revealed a reduction in number of spermatozoa to approximately 1/10 normal. A similar diet containing arginine, which followed the deficiency period, resulted in slow return of sperm number to the normal level. Hertz (*127*) demonstrated dietary impairment of estrogen response in immature monkeys. Samuels (*128*) has extensively reviewed dietary factors in relation to hormones.

Gassner *et al.* (*129*) fed a ration of 70 per cent sesame meal to cockerels during the second to fourth weeks of age and found testicular degeneration accompanied by decrease of comb growth. Supplementation of this diet with vitamin B_{12} produced testicular growth, differentiation, and comb development equal to, or greater than, those in controls. Since the failure of growth and development observed was characteristic of that seen after pituitary failure to produce adequate gonadotropins, there is the possibility that vitamin B_{12} is required for pituitary function.

Kendall *et al.* (*130*) observed sterility in rabbits fed on soy bean hay, and, on the basis of other experiments, the enzyme lipoxidase was suspected of being responsible. Nelson *et al.* (*131–133*), Hertz and Tullner (*134*) and Thiersch and Philips (*135*) have shown that tissue growth, including embryonic growth, is quantitatively dependent upon folic acid, and that anti-folic acid agents tend to interfere with such growth. Thiersch (*136*) administered 2 mg of aminopterin (an anti-folic acid agent), followed by 3 to 10 subsequent treatments of 1–2 mg at 12-hr intervals to human beings (the number of treatments depending upon the size of the patient and the age of the embryo or fetus), and obtained spontaneous abortions in 10 out of 12 cases.

Nelson *et al.* (*137*), referring to previous work, stated that studies had shown that the addition of a pyridoxine antagonist (desoxypyridoxine) to a pyridoxine-deficient diet resulted in a high incidence of fetal resorptions when normal adult rats were placed on such a diet 10 to 20 days prior to breeding, and that supplementation with pyridoxine on the day of breeding counteracted the adverse effects of the antagonist. They went on to show then that pregnancy in pyridoxine-deficient animals could be maintained to a significant degree by injection of 1 μg of estrone plus 4 mg of progesterone daily, but not by either hormone separately. They stressed that the results indicate an inadequacy of ovarian hormone secretion in pyridoxine-deficient animals.

Goldman (*138*) observed testicular atrophy and liver steatosis in cholesterol-fed hamsters.

Cosla (*139*) states that the action of ions and enzymes is as important in reproduction as that of the hormones, and that reproduction will fail to occur in certain plant forms in the absence of trace amounts of magnesium. Visscher *et al.* (*140*) found that animals maintained on diets containing trace amounts of certain metallic ions (Na, K, Ca, Mg) showed low reproductive performance, and that this condition could be corrected by adding α-tocopherol, or vitamin B_{12}.

Gassner *et al.* (*141*) refer to the work of Mann and co-workers and state that in the rabbit a close relationship exists between endocrine activity of the testis and the rate of fructose elaboration in accessory sex organs.

VIII. *Special Agents*:

Specific Compounds. Prior and Ferguson (*142*) administered the antibactericidal drug nitrofuran (20 per cent in the diet) to rats and obtained a condition of complete aspermia within 1 week. Similar results were obtained with furacin by Friedgood *et al.* (*143, 144*), who observed the effects in man in connection with cancer therapy. Nelson (*145, 146*) administered furadroxyl (1.5 mg/kg in the diet) to rats and obtained complete aspermia within 4 weeks. In all cases spermatogenesis returned to normal or higher levels after termination of treatments.

Lithospermum. Train *et al.* (*147*), in a study of utilization of desert plants of the Southwest, reported that certain American Indians used an infusion made from the desert plant *Lithospermum ruderale* as an oral agent for control of fertility, the women drinking a cup of this concoction once daily during periods when they wished not to conceive. Cranston (*148*) performed a series of experiments on mice and found that a fluid extract, mixed with normal diet, rapidly induced suppression of the estrous cycles in addition to lowering birth incidence in breeding females. Cranston suggested that the active factors derived from the herb act directly on the pituitary gland, suppressing release of gonadotropic hormones.

Suppression of estrous cycles with *Lithospermum* has also been observed by Drasher and Zahl (*149*), Zahl (*150*), Cranston *et al.* (*151, 152*), Plunkett *et al.* (*153*), Noble *et al.* (*154, 155*), Plunkett and Noble (*156*), Zahl and Nowak (*157*), and Weisner and Yudkin (*158*). Zahl observed that, whereas the sex organs go into a state of quiescence and increased fibrosis, removal of *Lithospermum* materials from the diet causes an immediate return to normal estrus and reproduction. No deleterious effects were observed in the pituitary, thyroid, suprarenals, or pancreas, and only passive fibrosis in the ovaries or uteri. Noble *et al.* (*155*) found the gonadotropin of pregnant mare's serum markedly susceptible to *in vitro* inactivation with crude *Lithospermum* extracts. This fact, combined with Zahl's observation that no histological changes are noted in the pituitary, suggests that *Lithospermum* may act by direct neutralization of gonadotropins. Attempts to obtain purified fractions of *Lithospermum* have not been successful.

Oil of Pisum Sativum. Nag (*159*) fed rats on a diet containing *Pisum sativum* for 8 months and obtained no young during this interval; however, when the *P. sativum* component was replaced by *P. areteneum,* litters were obtained.

Sanyal (*160, 161*) has developed an extract from the *P. sativum* which he states has fertility control action.

Sulfhydryl Groups. MacLeod (*162*) presents evidence indicating that —SH groups play an important role in the energy-producing mechanism of sperm, and that the motility and metabolism of human sperm are inhibited *in vitro* by substances which have an affinity for sulfhydryl groups.

Herbs. Historical accounts of the habits and practices of various primitive and remote peoples frequently make reference to concoctions taken orally for fertility control purposes. In a separate communication there is a list of more than 70 herbs used in such concoctions. Although many of these preparations have been dispensed by herb doctors and have been associated in one way or another with sorcery and witchcraft, it is possible that, through scientific studies, some will be found effective. *Lithospermum ruderale,* dealt with above, is an outstanding example of an herb used by primitive groups and later found fully effective by scientific groups.

IX. *Nervous Stimuli*:

Many experimental and clinical observations indicate that emotional states or other nervous stimuli produce changes in the female genital tract. In certain birds and in ferrets, light factors have been found to act by means of nerve pathways to induce pituitary secretion of gonadotropins (*163*), thus accounting for seasonal reproductivity. On the basis of these and other findings, commercially profitable methods of increasing egg-laying in chickens have been found. Of interest is the fact that nulliparous adult rats or mice can be induced to lactate by foster nursing. Studies by Ingelbrecht (*164*) indicate that lactation and anovulation may result from mammary manipulation.

In certain animals pseudopregnancy occurs. In the case of sterile matings or of mechanical stimulation of the uterine horns, corpora lutea persist in the ovary, and the uterine reactions simulate those which occur normally during the early stages of pregnancy, several estrous periods being missed. Anovulatory pseudopregnancy-like conditions accompany normal lactation and induce lactation as described above. In the rabbit, ovulation occurs as a rule only after the stimulus of coitus. Coitus may occasionally induce ovulation in the human female (*165*), and, in human beings, false pregnancy (pseudocyesis) is associated with psychic crises of various kinds (*166*). Friedgood (*167*) states that there is growing opinion that unconscious emotional conflicts constitute one of the etiological factors in sterility and that neuro-psychodynamic factors are of etiologic significance in impotence and amenorrhea as well as sterility.

All these conditions are initiated by nervous stimulation, including stimuli appearing to come from the subconscious mind, and they offer the prospect that reproduction may, under certain conditions, be controlled by nervous stimuli applied at the right time and in the right way.

X. *Rhythm*:

Of interest from the standpoint of fertility control is the rhythmic occurrence of ovulation. In the human female ovulation usually takes place near the middle of the menstrual cycle. Statistically, if coitus is avoided during the period of the ninth through the seventeenth days after the beginning of menstruation, the frequency of conception is reduced. Owing to irregularities in ovulation time in different individuals and also the lack of really satisfactory means of detecting the time of ovulation even in the same individual, however, use of the rhythm method of controlling fertility gives no real assurance of control. If a simple method were available that women could use to determine with certainty when ovulation occurs, the method would become much more reliable; furthermore, the period of avoidance of coitus could be reduced to 2 days or less, since the fertilizable life of the ovum is short (36 hours or less.

The suggested approaches for physiologic control of fertility are brought together here for more specific identification and for additional comment.

1) *Estrogens and Androgens*: These agents can be administered orally or injected into males or females; they prevent pituitary secretion of FSH and thereby prevent follicle growth in the female and spermatogenesis in the male. Minimal doses, the most effective patterns of treatment, and the full significance of side effects have not yet been determined. The view prevails among clinicians that large doses of estrogens or androgens are required to prevent ovulation. Certain animal evidence suggests the possibility of control with dosages within the limits of the physiologic range.

2) *Progesterone*: This agent can be given to females and prevention of ovulation obtained; but, as in the case of estrogens and androgens, minimal doses, the most effective treatment patterns, and the extent of side effects are not known.

3) *Prolactin*: Prolactin, administered orally or injected into females, is believed to result in increase of progesterone output and in inhibition of pituitary secretion of LH, thereby preventing ovulation; detailed information is lacking.

4) *Pregnanediol* (non-estrogenic fraction): This end product of progesterone metabolism is antagonistic to progesterone, and its use prevents decidual growth and might be expected to prevent ovulation or implantation or both; little is known as yet about its practical value for fertility control.

5) *Anti-gonadotropins*: Bodies immune to pituitary gonadotropins can be created to prevent follicular growth and ovulation; requirements for effective control and practical means of supply of agents have not been developed.

6) *Phosphorylated Hesperidin*: This agent is believed to act by preventing dispersion of follicular cells around the ovum, thereby preventing fertilization. Positive fertility control results based on studies in animals and human beings have been reported. Some information about dosages and patterns of treatment is available. If previous findings can be repeated, further developments are needed to reduce the required frequency of medication.

7) *Spermatotoxins*: Bodies immune to the protein materials of sperm from the same or other species have been obtained; both positive and negative results have been obtained with respect to control of fertility by means of spermatotoxins. Validity of the approach remains in question.

8) *Wharton's Jelly*: Positive fertility control results have been obtained in preliminary experiments utilizing crude extracts of Wharton's Jelly as antigens. Confirmation of the results is needed.

9) *Microorganisms*: Evidence indicates that bacteria or yeasts, which sometimes exist unnoticed in the vagina or uterus, are responsible for infertility. Tests are needed to determine whether such organisms can be transmitted from one patient to another without harm, and whether they can be relied upon for fertility control.

10) *Nitrofurans—Furacin and Furadroxyl*: Preliminary experiments indicate that these agents stop

spermatogenesis in the miotic phase. More experiments are needed to determine their practical value.

11) *Lithospermum*: Crude extracts of the desert plant *Lithospermum ruderale* are reported to have been used by Indians of the Southwest as oral contraceptives. Animal experiments confirm the fact that this agent stops ovulation. Additional developments are needed to purify and standardize the active ingredient, and to test for deleterious side effects.

12) *Extracts of Pisum sativum*: Preliminary experiments indicate that substances from the garden pea prevent fertility. Confirmation studies are needed.

13) *Vitamin A Deficiency*: Prolonged gestation and difficult parturition have been shown to result from lack of vitamin A in the diet.

14) *Vitamin E Deficiency*: Successful gestation has been found to depend upon vitamin E.

15) *Vitamin B_{12} Deficiency*: Testicular degeneration has been shown to occur as a result of the absence of vitamin B_{12} from the diet.

16) *Arginine Deficiency*: Amino acid content in sperm is high. Absence of arginine in the diet has been shown to result in formation of ineffective sperm.

17) *Folic Acid Deficiency*: Folic acid is a requirement for successful gestation. Anti-folic acid agents cause a termination of development.

18) *Metallic Ion Deficiency*: Animals maintained on diets lacking in certain metallic substances show low reproductive performances.

19) *Nervous Control*: Certain sensory and psychic stimuli interfere with the reproductive process. No practical methods have been developed for utilizing this type of information.

20) *Rhythm*: If the time of ovulation is known, the opportunity for fertilization can be avoided. No simple means of determining ovulation has as yet been developed.

Twenty leads for physiologic control of fertility have been listed. Other leads could be drawn from the material presented, and still others could be drawn from literature not mentioned here.

In a general way, the various approaches fall into research categories as follows:

1) *Hormone and enzyme research*, involving estrogens, progesterone and related compounds, androgens, anti-hormones, anti-enzymes, and other substances affecting the mechanism of control of fertility; also agents which have a highly specific effect such as the nitrofurans, aminopterin, and phosphorylated hesperidin.

2) *Immunological research*, involving studies of spermatoxins, Wharton's Jelly, and the like.

3) *Symbiotic organism research*, involving bacteria, yeasts, and other organisms which inhabit the reproductive organs and cause temporary infertility.

4) *Fluid physiology research*, involving media of the Fallopian tubes, cervical mucus, and semen.

5) *Dietary research*, involving vitamins, anti-vitamins, substrate materials, metallic ions, and special substances of various kinds.

6) *Neuro-hormone research*, involving psychic and sensory stimuli acting upon the endocrine system.

7) *Rhythm research*, involving the determination of fertile and infertile periods in the menstrual cycle.

The work in relation to nearly all approaches divides naturally into four stages:

1) *Animal studies*: to test the soundness of approaches.

2) *Biochemical development*: to purify and standardize agents and make them available at low cost.

3) *Clinical investigations*: to determine the reliability of methods in human beings, minimal doses, and the most effective patterns of treatment.

4) *Pilot testing*: to determine methods of achieving utilization of fertility control procedures.

Some of the existing leads (phosphorylated hesperidin, progesterone, *Lithospermum*, and aminopterin) are at a point of development where pilot testing becomes a matter requiring consideration; some have been used in human beings for fertility control purposes with varying degrees of success (phosphorylated hesperidin, aminopterin, spermatoxins, Wharton's Jelly); some represent by-products of experiments carried out for other purposes; and some represent preliminary research leads only.

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News and Notes

Tropical Building Design and Construction Symposium

THE symposium, "Scientific Principles and their Application in Tropical Building Design and Construction," held under the auspices of the UNESCO Science Co-operation Office for South Asia (SASCO) and the National Institute of Sciences of India (NISI), was the outcome of the collaboration of these two bodies, with substantial assistance from several technical departments of the Government of India, which furthermore made a generous financial contribution to its fund.

A strong Organizing Committee, which, with various sub-committees was responsible for the details of the arrangements, was appointed with representatives of the Government of India in the Ministries of Housing, Works and Supplies; Natural Resources and Scientific Research; Defense; the Council of Scientific and Industrial Research; and of a number of professional institutions and industrial organizations interested in building, construction, and housing problems. J. L. Sarin, of NISI was the secretary of the committee.

Approximately 150 delegates from India, Burma, Ceylon, and Indonesia, attended the symposium. Foreign consultants invited by UNESCO from England, Holland, and Israel, were present to guide its deliberations, and observers from various United Nations organs and specialized agencies participated in the meetings.

The opening session took place in the auditorium of the National Physical Laboratory of India, New Delhi, December 21, 1952. It was inaugurated by the Prime Minister of India. On this occasion, Shri K. D. Malaviya, Deputy Minister of Natural Resources and Scientific Research, S. L. Hora, president of NISI, and P. C. Young, head of SASCO, also delivered addresses. Messages were delivered by foreign delegates on behalf of their countries, Ceylon, Burma, and Indonesia; and by the representatives of ILO, WHO, and ECAFE. In the afternoon, leading technical papers were read by Indian and foreign experts on subjects covering practically the entire field of the symposium. Afterwards, the delegates were the guests at a reception given jointly by SASCO and NISI.

On subsequent days, the symposium met in five sections dealing with (1) Design and Planning, (2) Materials, (3) Production and Building Practice, (4) Ancillary Services for Sanitation, Comfort, and Public Health, and (5) Research, Testing, Documentation, and Technical Training. Attendance at these section meetings was good (about 150 on the average). The total number of complete papers submitted was 80, of which two-thirds were by experts from within the region itself and one-third from the consultants or other foreign specialists. Over 20 written précis of papers which were not, however, later communicated to the organizers, were also received. As far as possible the papers were mimeographed and distributed beforehand. Thus most of the time at the session was left free for the discussion. One point which became apparent was that scientific workers and engineers in