# Biology Today

## New Developments in Reproductive Biology

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*Department Editor*

I've just finished teaching a two-week course in reproductive biology. It's an intensive course; my students and I spend over four hours together each day. But it's an experience that I, at least, enjoy. During this time, it's the only course I teach and the only course my students take, so we're not distracted by other subjects. We can delve deeply into one field, and an exciting field at that. This is the third year I've offered this course, and it changes more from year to year than any other I teach. There is so much research being done in reproductive biology that every week important new findings are forthcoming. I'm devoting this month's column to some of the information that made this year's course different from last year's.

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### Sex Differences in the Brain

Exactly how different biologically are women and men? The dissimilarities in reproductive structures and functions are obvious, but what about the rest of the body? Every male and female has a heart and a brain and an immune system; are these identical in the two sexes? Women develop atherosclerosis at a later age than do men, possibly because of the protection female hormones provide before menopause. But women are more susceptible to autoimmune diseases, including multiple sclerosis and systemic lupus erythematosis, perhaps because they have two X chromosomes that carry several genes involved with immune function. Disclaimers like "possibly" and "perhaps" are used in discussions of non-reproductive sex differences because our knowledge is so scanty. There is no place where these disclaimers are more needed than in discussions of sex differences in the human brain.

There are at least two reasons for this. Most of the studies on brain differences have been done with animals: rodents, birds, nonhuman primates. Extrapolating from animals to humans is always difficult, but may be impossible where behavior is involved. Even results from human experiments are difficult to interpret because so much human behavior is learned rather than biologically controlled; it's hard to tell when Nature or nurture is playing the more important role.

It is well established that gonadal steroids affect fetal development of the preoptic area of the hypothalamus. This structure controls the release of reproductive hormones from the pituitary and influences reproductive behavior, at least in animals. Now many investigators are discovering differences in the cerebral cortex as well (*The Sciences*, March 1981). In all humans, the dominant cerebral hemisphere, in right-handed individuals the left hemisphere, controls language ability, while the nondominant hemisphere deals with spatial perception. But this asymmetry may not be quite the same in the two sexes. In studies of cognitive abilities, males do better in tests of mathematical reasoning and spatial relationships—nondominant hemisphere functions. Females score higher on verbal ability tests; these involve dominant hemisphere functions. There is also evidence that the male brain is more functionally asymmetric than the female brain. Damage to the dominant hemisphere in males affects verbal functioning, while damage on the other side disorders nonverbal abilities. In females with localized cerebral injury, this asymmetry is less pronounced.

If these sex differences are real, what causes them? The best answer is the presence of sex hormones during fetal development, at puberty, or at both times. New evidence supporting this comes from a study of men whose testosterone levels are abnormally low because throughout life the hypothalamus fails to stimulate the pituitary to release gonadotrophins (*The New England Journal of Medicine*, May 20, 1982). These individuals have male external genitalia and are

therefore raised as males, but they fail to go through puberty. Their performance on spatial ability tests is similar to that of females rather than males. Men with the smallest testes, and therefore presumably the lowest hormone levels, scored the lowest on these tests. Even after androgen-replacement therapy, their scores didn't improve. Men whose testosterone levels were normal during puberty but decreased later in life had spatial ability scores comparable to those of normal males. So it appears that the presence of androgens either during fetal development or at puberty, rather than their continued presence, determines spatial ability.

In the same issue of *The New England Journal of Medicine*, there is an editorial by Jerome Kagan in which he cautions against accepting too hastily the hypothesis of hormonal influence of spatial ability. The sample size in this study was small, and there was no matching for such possibly important factors as social class and years of formal education. Kagan points out that spatial ability is not a unitary skill, and therefore is difficult to measure accurately. Also, the tests used to judge it are scored not only on correct performance but on speed of performance which, again, makes results difficult to interpret. Finally, sex differences in spatial perception aren't universal; they don't exist among adults in isolated, rural communities.

Whether or not biologically based sex differences exist is an intriguing question, and some think, a frightening one. Answers would be valuable, no matter what they are, but much more research is needed. It would be valuable if the results were always accompanied by critiques as perceptive as Kagan's.

## A Versatile Hormone

Luteinizing hormone-releasing hormone (LHRH), produced by the hypothalamus, controls the pituitary's release of its two gonadotrophic hormones, FSH and LH. Thus, LHRH, characterized in 1971 as a ten-amino acid polypeptide, is the hormone in charge of the reproductive system. Because of this, LHRH has been extensively studied during the past ten years. That research is now bearing fruit in the form of practical uses for LHRH and its derivatives.

Buserilin, an LHRH agonist with a slightly different amino acid sequence and a great deal more potency, is being used in the treatment of advanced prostate cancer (*Lancet*, May 15, 1982). For reasons not well understood, powerful LHRH agonists inhibit the pituitary's release of FSH and LH rather than stimulate it as the hormone naturally does. They decrease the activity of the reproductive system and thus the release of testosterone, which stimulates the growth of prostate cancer. So these agonists can be used instead of castration to slow or even reverse the development of prostate carcinoma. When treatment is finished, the hormone levels rise to normal again, thus avoiding the long-term effects of castration. Similar studies are being conducted on women with advanced breast cancers that are dependent on estrogen for growth (*Lancet*, May 29, 1982).

LHRH agonists are also being investigated as possible contraceptives (*Nature*, April 1, 1982). Daily injections of an LHRH agonist inhibit ovulation, and thus progesterone production. They also produce variable and unpredictable changes in estrogen levels; some women produce too little and develop menopausal symptoms, others produce too much, which can lead to proliferation of the endometrium.

Administering LHRH agonist only at specific times in the cycle may overcome these problems. If the agonist is given at mid-cycle, the luteal or secretory phase is decreased making it impossible for an embryo to implant in the endometrium. If the agonist is given in the late luteal phase, it causes disruption of the corpus luteum which leads to a fall in progesterone levels and menstruation. Injection of an LHRH agonist on three successive days at the time of menstruation induces a shortened luteal phase and below normal levels of estrogen and progesterone (*Science*, January 8, 1982).

This confusing array of schemes illustrates how uncertain researchers are of the path to follow. Work must be done on scheduling and side effects as well as on the underlying control mechanisms. If they understood why high levels of LHRH and its agonists have an inhibitory effect, they might be able to manipulate this system more safely and efficiently. But some progress has already been made on more practical problems. Originally, LHRH agonists could only be administered by injection which would be impractical for a contraceptive. Now a nasal spray has been developed, though larger doses are needed when the drug is given in this form.

LHRH agonists are also being investigated as male contraceptives. Daily injections reduce sperm counts drastically; testosterone levels also decrease, leading to loss of libido. While testosterone replacement may relieve this problem, much research is needed to determine whether or not an LHRH contraceptive would ever be practical for widescale use by men.

## Another Contraceptive

A novel approach to contraception has been reported by a French biochemist, Etienne-Emile Baulieu (*The New York Times*, April 20, 1982). He has developed a steroid that blocks the progesterone receptors of uterine cells. If the drug is taken for four days, beginning two days before menstruation is expected, it causes a sloughing off of the endometrium comparable to what happens in normal menstrua-

tion. This will occur even if the egg is fertilized. The drug's advantages are that it is only given for four days each month, and that it does not change circulating levels of estrogen and progesterone as do the birth control pills now in use. But this drug is not without side effects. It may increase menstrual flow and reduce adrenal hormone production.

## Tricking the Immune System

An embryo is really a mass of foreign cells growing in the uterus. How does the immune system tolerate this invasion? Several mechanisms are probably involved. The embryo is covered by a dense layer of decidual cells which enclose it soon after implantation; this layer cuts off the drainage of lymphocytes to maternal tissues. There is also a nonspecific suppression of lymphocytes by several hormones, including chorionic gonadotrophin, progesterone, and prolactin (*Scientific American*, August 1980). New studies with rabbits reveal that a protein called uteroglobin on the surface of embryonic cells prevents the immune system from recognizing those cells as foreign (*Science News*, January 16, 1982). Uteroglobin isn't made by the embryo for its own defense; it's produced by the uterus along with the enzyme, transglutaminase, which catalyzes the attachment of uteroglobin to the embryonic cells. Rabbit prostate secretions also contain these two proteins which may protect sperm from immune attack in the female genital tract.

## The Physical Causes of Impotence

Men suffering from impotence have long had their problem treated as an emotional one. It is true that psychotherapy or couple-based sex therapy has cured many, but doctors are now convinced that a large number of cases have an organic basis (*The New York Times*, May 18, 1982). In one study of impotence, a third of the men suffered from hormonal abnormalities —either high prolactin levels which decrease testicular function or low testosterone levels.

Many other physical problems can also cause impotence. By damaging arteries, diabetes and atherosclerosis can interfere with blood flow to the penis and prevent erection. In priapism, the erectile tissue is damaged by blood trapped in the penis. The nervous control essential for erection can be disturbed by many drugs, including narcotics, reserpine used in treating hypertension, MAO inhibitors prescribed as antidepressants, and, of course, alcohol.

Understanding the physiological basis of impotence will lead to better treatment. Hormonal therapy has proved effective in cases of hormonal abnormalities, and bypass surgery to increase penile blood flow is being considered. Where treatment is ineffective, penile implants—either a new inflatable implant or one which is bendable—can be used successfully.

## GRID

GRID, gay-related immunodeficiency disease, is a rare but disturbing syndrome with many different manifestations (*The New England Journal of Medicine*, December 10, 1981). About 350 people, mostly homosexual men, have been diagnosed as having GRID; almost half of these cases have been fatal. GRID seems to involve a total collapse of the immune system leading to infections, autoimmune diseases, cancer, or a combination of these. The infections are opportunistic. They usually arise only in those with reduced resistance to disease, for example, those taking immunosuppressive drugs. These infections include cytomegalovirus, the fungal infection toxoplasmosis, and an

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male and female fruit flies, the student will:

1. Hypothesize the location of certain genes.
2. Determine the sex of each of the samples.
3. Hypothesize the eye color phenotype and genotype of given samples.
4. Hypothesize a ratio of possible fruit fly offspring for eye color and sex.

### Activity: "The Fruit Fly Chromosome Mystery"

Below are the sex chromosome maps of five different fruit flies. The X chromosome contains the gene for eye color. The red-eye gene is the allele to the white-eye gene and is dominant over the white-eye gene. The Y chromosome contains no genes. Fly D has white eyes. The gross structure of the sex chromosomes in the fruit fly is similar to that of humans. Your task is to unravel the following mysteries:

1. Where is the location for eye color on the chromosome map?
2. What is the sex and eye color of each individual?
3. What are the genotypes for sex and eye color for each individual?
4. What is the ratio of possible offspring between Fly C and Fly D?

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often-fatal form of pneumonia caused by the protozoan, *Pneumocystis carinii*. Other forms of GRID involve autoimmune diseases such as lupus and various cancers including Burkitt's lymphoma, cancers of the tongue and anus, and Kaposi's sarcoma, a malignancy of the immune system. Kaposi's sarcoma is particularly alarming because it is rapid-developing and frequently fatal.

No one is sure what causes GRID or why it has suddenly appeared now. Most, though not all, cases have been among homosexual males who had a large number of sexual partners and who used sexual stimulants such as amyl nitrite as well as illicit drugs. Though some suspect that nitrites are involved, the evidence isn't overwhelming. Others think the immunosuppression and cancers are linked to infection with cytomegalovirus. Some even feel the semen itself may be responsible since it can be a potent immunosuppressive if it gets into the bloodstream. Finally, over-the-counter cortisone creams used for skin irritations may suppress immunity because membranes of the anus and genitals readily absorb the cortisone. This last explanation would account for the sudden appearance of GRID because these creams have only become available recently. Some physicians don't think GRID is a new disease at all, but one that is just being more readily identified.