Infertility: Promising New Treatments

The infertile, traditionally a silent and unpublicized group, have been getting a lot of attention of late. This attention was sparked by the first successful human in vitro fertilization and the subsequent birth of Louise Brown in July of this year. Other methods, however, including new drugs and delicate surgical procedures, are enabling many couples with previously untreatable infertility to have children.

There are no good data on the incidence of infertility. The American Medical Association estimates that 15 percent of all married couples in this country are unable to have any children and an additional 10 percent have fewer children than they wish. However, these figures are only gross estimates since, as Emil Steinberger of the University of Texas at Houston points out, there is not even a good definition of infertility. He explains that, "In animal husbandry, a female in heat failing to conceive after one or two exposures to a fertile male is automatically considered infertile. A human female may be exposed to the male for several years in the course of several dozen ovulatory episodes, may conceive on only one occasion, and still be considered fertile."

Although often only one member of an infertile couple seeks medical treatment, infertility is a problem of couples. Infertility specialists who see both members of infertile couples say that almost always neither is fully fertile. But often, neither would have a noticeable fertility problem if wed to a more fertile mate.

Most of the new treatments of infertility are aimed at women. This is not because researchers are unaware that men are equally likely to be infertile, but rather that so little is known about what goes wrong when men are infertile. "The problem," says Steinberger, "is that we can't *diagnose*. If we could diagnose, we could probably correct many cases of male infertility with treatments now available."

The new treatments of women correct the two major causes of female infertility: failure to ovulate and obstruction of the Fallopian tubes.

A large number of women fail to ovulate because they secrete excessive amounts of the hormone prolactin, a condition known as hyperprolactinemia. According to John Tyson of the University of Manitoba, as many as 28 percent of women with menstrual abnormalities have hyperprolactinemia. It is not yet known exactly how high prolactin concentrations in the blood inhibit ovulation nor why so many women have hyperprolactinemia. But a significant number of women with this disorder may soon be treated with a new drug, bromocriptine mesylate (Parlodel), that became available in the United States on 1 August of this year. Bromocriptine binds to dopamine receptors on the anterior pituitary and simulates the effects of dopamine, a neurohormone that inhibits prolactin secretion.

Many infertility specialists are hailing the recent availability of bromocriptine and are saying quite frankly that they intend to use or are already using the drug to treat infertility. Bromocriptine, however, has not been approved for the treatment of infertility. In fact, the package insert says, "patients should be required to use contraceptive measures" while taking the drug. U.S. patients are required to use contraceptives because it is not yet known whether bromocriptine produces birth defects. Nonetheless, a number of investigators point out that the drug has been used for years in Europe for the treatment of infertility. There is no evidence of increased incidences of birth defects among the more than 400 babies born to women who took the drug. (However, this is thought to be an insufficient sample to detect birth defects.)

The approved use of bromocriptine in the United States is for the short-term treatment of women who have both amenorrhea (failure to ovulate) and galactorrhea (milk in the breasts). For this disorder, the drug has been shown to be highly effective. Pooled data from 22 separate studies with a total of 226 patients indicate that 80 percent began menstruating within 6 weeks of taking bromocriptine. Galactorrhea was greatly diminished or reduced in 75 percent of the patients within 7 to 13 weeks after starting treatment. However, bromocriptine is only effective while it is being taken. It does not cure the underlying pathology producing hyperprolactinemia.

The problem with the approved use of bromocriptine is that no one plans to prescribe the drug for patients with amenorrhea and galactorrhea who do not wish to become pregnant. William Westlin of Sandoz Pharmaceuticals, which produces bromocriptine, says, "We have received letters from physicians asking why the drug is even on the market if it can't be used for infertility. I have a hard time answering that question." Westlin concedes that, "It's obvious that the drug's primary use is for treating infertility. To put the drug on the market for amenorrhea accompanied by galactorrhea but not for infertility is kind of ridiculous." Westlin says that Sandoz is now conducting studies in this country of the safety and efficacy of bromocriptine for treating infertility. The results, however, will not be in for several years.

Michael Thorner of the University of Virginia is one of a number of investigators who are disturbed by the restrictions on the use of bromocriptine in the United States. Thorner has had extensive experience in England with the use of bromocriptine to treat infertility. He views the approved use of the drug in this country as only "the tip of the iceberg," explaining that the drug not only alleviates hyperprolactinemia when it is accompanied by galactorrhea but also when it is not. He says that 70 percent of women with hyperprolactinemia do not have galactorrhea. Both groups of women can become pregnant when they take the drug. Moreover, there are a number of infertile women who have hyperprolactinemia but not amenorrhea and these women, too, can be treated with bromocriptine.

Another group of women that Thorner and others think may be helped by bromocriptine are women with pituitary tumors. These tumors secrete excessive amount of prolactin, and their secretion of prolactin can be prevented by bromocriptine. There is no evidence that bromocriptine can shrink the size of the tumors, but Thorner contends, and others agree, that surgery alone may not successfully lower prolactin secretion to normal or restore fertility, whereas bromocriptine can enable women with small tumors to become pregnant. However, there is a slight risk that these tumors will grow, causing visual problems during pregnancy. Richard Falk of Georgetown University and Columbia Hospital for Women in Washington, D.C., points out that no one yet knows whether the very small pituitary tumors being detected with newer and more sensitive methods will ever grow to a

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substantial size. It is not clear that these tumors should be surgically removed.

Since bromocriptine has proved useful only for women with hyperprolactinemia, it is not always suitable for inducing ovulation. Many women fail to ovulate and yet have normal amounts of prolactin in their blood. Often these women can be made to ovulate by the standard treatments with clomiphene citrate (Clomid) or human menopausal gonadotropin (HMG).

Clomiphene citrate is the drug of choice for women who do not have hyperprolactinemia, because it is less likely than HMG to over-stimulate the ovaries. Clomiphene binds to estrogen receptors on the hypothalamus and prevents estrogen from binding there. The hypothalamus then senses what seems to be a drop in estrogen concentrations and responds by causing the pituitary gland to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These two hormones act on the ovaries, causing ovulation. According to Abba Kastin of the Veterans Administration (VA) Hospital in New Orleans and Tulane University, 30 percent of women who take clomiphene citrate ovulate and become pregnant.

When women do not respond to clomiphene, HMG (Pergonal) is often prescribed. This is a substance extracted from the urine of postmenopausal women. The reduced production of estrogen after menopause causes the hypothalamus to constantly signal the pituitary to release FSH and LH. The substance HMG is rich in FSH and also contains some LH. These hormones, when given to women who fail to ovulate, act directly on the ovaries, preparing them for ovulation. The problem with HMG, however, is that it can overstimulate the ovaries, causing several eggs to be released at one time. In some cases the ovaries can be so over-stimulated that they become as large as grapefruits, and this can be a life-threatening situation.

Andrew Schally of the VA Hospital in New Orleans and Tulane University together with Kastin and their associates are developing a somewhat gentler way to stimulate the ovaries. They give the women a synthetic analog of luteinizing hormone releasing hormone (LHRH). This hormone acts on the pituitary, causing LH to be released. Presumably, it should prevent over-stimulation of the ovaries because the pituitary would release only the appropriate amount of LH.

The New Orleans group first began using LHRH to induce ovulation in 1971. Subsequently, they developed a long-acting analog of the hormone and began giving it either orally or by nasal spray to anovulatory women. According to Kastin, about 30 percent of their patients ovulate when given LHRH, but the ideal dosage and mode of administration have not yet been found. The work on LHRH has attracted the attention of a number of investigators, including D. Lynn Loriaux of the National Institute of Child Health and Human Development (NICHHD). Loriaux plans to begin a clinical trial comparing the use of HMG to that of LHRH in the treatment of anovulatory women who have been referred to the NICHHD infertility clinic and who do not respond to clomiphene.

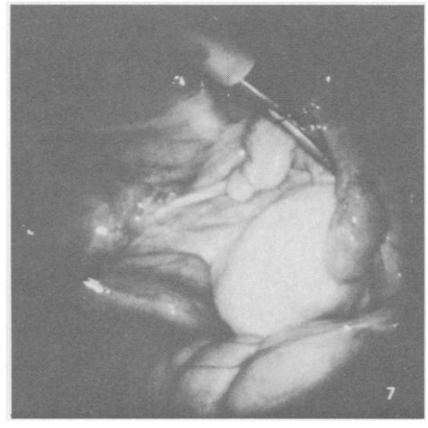

Fig. 1. The cut end of a Fallopian tube from a woman who was sterilized by a tubal ligation. The white oval structure on the right is an ovary. [Source: Richard Falk, Georgetown University and Columbia Hospital for Women]

Almost as common a cause of infertility as failure to ovulate is blocked Fallopian tubes. Falk estimates that as many as 40 percent of infertile women referred to him have blocked tubes. Tubes can become obstructed because of infections or because of voluntary sterilization.

Within the past 2 years, a number of investigators have been very successful at reconstructing blocked Fallopian tubes with "microsurgery." This technique, which was developed by David Garcia and Luigi Mastroianni at the University of Pennsylvania, is nothing more than surgery in which a microscope is used to magnify the surgical field from 4 to 25 times, enabling surgeons to clearly view the three layers of the tubes. In a tedious 4-hour operation, surgeons cut the obstructions from the tubes and sew up the tubes, one layer at a time. The use of the microscope enables them to use a very small needle and fine suture, which minimizes the damage done to the tubes. Previously, surgeons just looped stitches around the outer edges of the tubes and allowed the layers of the tubes to grow together.

There is a consensus among infertility specialists that microsurgery has significantly increased the success rate of Fallopian tube reconstructions. (Success is defined as a term pregnancy.) Good data on the success of this procedure, however, are not yet in. Moreover, the success rates with microsurgery vary depending on how badly damaged the tubes are. Mastroianni points out that the microscope is only useful when there are small obstructions at the narrowest end of the tube—the end nearest the uterus. Safa Rifka, who works with Falk, estimates that fewer than half of all women with tubal obstructions can be successfully treated with microsurgery.

The best candidates for tubal reconstructions are women who have been sterilized by having a section of their tubes looped out and tied. The looped-out portion falls off, producing what Falk describes as "a good clean break in the tube" (Fig. 1). Falk estimates that the success rate for microsurgery on these women is 75 percent. He points out that as many as 15 percent of women who have been sterilized by tubal ligation subsequently want their sterilizations reversed.

The worst candidates for microsurgery are women who had extensive tubal infections such as those caused by gonorrhea. These women have only a 20 percent chance of becoming pregnant after the surgery, according to Falk, and even if they do become pregnant there is a good chance that the embryo will become embedded in the tubes rather than in the uterus. Such an ectopic pregnancy ends in the rupture of the tube and a spontaneous abortion accompanied by what may be a life-threatening hemorrhage. Nonetheless, Falk and Rifka report that virtually all of their patients with extensive tubal infections opt for microsurgery.

Many women have tubes so badly damaged that microsurgery cannot correct them. These women can only become pregnant by means of in vitro fertilization—a technique whose success rate may be quite low and whose feasibility was only recently shown.

In marked contrast to the successful treatments of the most common causes of female infertility, there are as yet few treatments for most infertile men. In fact, investigators find it difficult even to decide on criteria for defining male infertility. Both sperm count and "quality" of sperm are important, but it now seems likely that fertile men can have far fewer sperm than previously thought necessary

and that men with marginal semen quality can still be fertile.

Definitions of how many sperm are necessary for fertility have ranged widely. Commonly accepted numbers vary from 60 million to 20 million sperm per milliliter of semen. The American Fertility Society cites over 20 million sperm per milliliter of semen in an ejaculate of 3 to 5 milliliters as the minimum for normal fertility.

Recently, Keith D. Smith of the University of Texas Medical School in Houston and Steinberger evaluated these definitions of "normal" sperm counts by studying the sperm counts of more than 4000 men requesting vasectomies. They report that more than 41 percent had fewer than 40 million sperm per milliliter of semen; 19 percent, fewer than 20 million per milliliter; and 54 percent, fewer than 100 million per ejaculate. (A normal ejaculate is 3 to 5 milliliters of semen.) Steinberger and Smith believe that the definition of what is too few sperm for fertility may turn out to be fewer than 10 million sperm per milliliter of semen. This is not to say that men with few sperm are just as fertile as those with many. However, men with few sperm may not be as infertile as they were previously thought to be.

Richard Sherins and his associates David Brightwell and Phyllis Sternthal of NICHHD similarly find that previous estimates of sperm necessary for fertility are too high. In their analysis of 119 men referred to them because of infertility, they found that men who had as few as 27 million sperm per ejaculate could still impregnate their wives. Moreover, Sherins points out, men who have had only 2 to 5 million sperm per ejaculate have impregnated their wives. Both Sherins and his associates and Steinberger and his associates find that at least 50 percent of the wives of men referred to them for infertility have tubal obstructions or are not ovulating normally. Often pregnancy results when the wives alone are treated. Commenting on this situation, Sherins says, "Most husbands of barren marriages should be considered fertile unless proven otherwise."

Unlike the quantity of sperm in semen, which can be easily measured, the quality of sperm is an elusive concept. It is generally defined to be a measure of how motile the sperm are and whether their morphology is normal. A number of infertility specialists report that men whose sperm have poor motility or morphologies tend to be infertile. However, not even these indications of quality are definitely established. Sherins and his associates find, for example, that the sperm motilities of fertile men are not always very great and that sperm motility often varies considerably from ejaculate to ejaculate. A better indicator of sperm quality, they say, is morphology.

Men with a large proportion of abnormally shaped sperm may be infertile because the abnormally shaped sperm contain defective chromosomes. According

The Psychology of Infertility

Most people, when told they have a medical problem that does not affect their health in any major way, react calmly and feel no hesitation in discussing their medical history with friends. That is, they react calmly to knowledge of all minor medical problems except infertility. There is something psychologically ravaging about infertility, something that brings out extreme behavior in many patients.

Richard Falk of Georgetown University and Columbia Hospital for Women in Washington, D.C., recalls that two of his female patients committed suicide when told that they could never have children. Other patients objected strenuously to the word "fertility" on the return address of the bills sent out by Falk's clinic. These patients did not want their letter carriers to guess they were infertile.

Men as well as women have strong emotional reactions to their infertility. Many men refuse even to have sperm counts when it is suspected that they may be infertile. However, there are few treatments for infertile men (see main story). The bulk of the medical treatments of infertility are directed toward women.

The extent to which many women go to become pregnant is truly heartrending. D. Lynn Loriaux, director of the infertility clinic at the National Institutes of Health, explains that the diagnosis and treatment of infertility are routinely slow and frustrating and are quite often expensive.

After months of testing to establish whether a woman ovulates and whether her ovaries, Fallopian tubes, and uterus are normal, doctors usually try to induce ovulation with clomiphene citrate—a drug generally taken as a pill for 5 days a month. If clomiphene does not work, they sometimes find that they must resort to treatment with human menopausal gonadotropin (HMG) and human chorionic gonadotropin (HCG) to induce the woman to ovulate. A woman who undergoes this treatment must see her doctor each day for the first 10 to 14 days of the month. She is given an injection of HMG at each visit to stimulate her ovaries. She also has blood drawn and has a pelvic examination at each visit. The blood is analyzed for estradiol, which provides an indication of how her ovaries are functioning, and the pelvic examination is used to determine whether her ovaries are enlarged, which would indicate that they are over-stimulated. After the HMG has properly stimulated the woman's ovaries, she is given an injection of HCG to cause her to ovulate.

"This process is repeated month after month until the women become pregnant or run out of money," Loriaux says. The process is expensive, costing from $450 to $800 a month to induce ovulation with HMG and HCG. Moreover, the women run the risk of producing too many eggs and having multiple pregnancies which cannot be sustained. Loriaux recalls instances in which patients who decided to have abortions when, after being treated with HMG and HCG and becoming pregnant, it was discovered that they were carrying five or six embryos.

Although most women being treated for infertility truly want children, there are some extreme cases in which women want primarily to become pregnant. For these women, the state of being barren rather than the state of being childless is what is devastating. An incident that occurred recently at Falk's office graphically illustrates the difference between wanting to be fertile and wanting to have a child. A television producer arrived to film an operation in which a woman was to have a sterilization reversed. The producer also wanted to interview a woman who had already had a sterilization reversed and now was pregnant. Falk's secretary called a former patient to see if she would consent to be interviewed. The patient, however, said she could not be interviewed because, although she had indeed become pregnant, she had had an abortion.—G.B.K.

to Andrew Wyrobek of Lawrence Livermore Laboratories, the shapes of sperm seem to indicate their genetic content. For example, mice exposed to known teratogens subsequently produce abnormally shaped sperm. Abnormally shaped sperm may be unable to fertilize an egg, or if they do fertilize an egg, the resulting embryo may not be viable. This should not be taken to mean that normally shaped sperm necessarily have normal chromosomes, Wyrobek points out. When the proportion of abnormally shaped sperm in a semen sample is high, all the sperm in the sample are more likely than usual to have defective chromosomes. Wyrobek notes that men with certain genetic diseases, such as cystic fibrosis, tend to produce sperm with poor morphologies and in one case, two brothers who were infertile both had only abnormal round-headed sperm.

There are a few specific conditions causing male infertility that can be corrected, but, according to Steinberger, what researchers need is "a very careful, fundamental study of the male reproductive system." As of now, the best hope for treating infertile couples is to correct female infertility.—GINA BARI KOLATA

Isotopic Anomalies in Meteorites: Complications Multiply

For more than 5 years, cosmochemists and astrophysicists have been considering the possible implications of the isotope chemistry of meteorites for the creation of the solar system. The simple existence of variations in the isotopic composition of meteorites demonstrated that, contrary to the assumptions of the previous 20 years, the ball of gas and dust that evolved into the sun and planets was not a thoroughly mixed, homogeneous collection of all the final ingredients of the solar system; some additions of unusual isotopic composition had not been completely stirred in before the rocks of the meteorites formed.

More recently, strong evidence has suggested that not only did some exotic material fail to mix in completely, but at least one isotope had only shortly before been synthesized from other elements. All elements heavier than helium must have been created in processes associated with the lives and deaths of stars other than our own, but there had never been any reason to suppose that such processes occurred close to the time (within 1 million years) and place of the solar system's creation. Now, a hypothetical nearby supernova has gained favor as a possible trigger for the collapse of the presolar nebula and as a site of new element synthesis (*Science*, 21 May 1976, p. 772). But the mushrooming number of elements with anomalous isotopic compositions discovered in the last year has been associated with numerous possible nucleosynthetic processes, not all of which bear an obvious relation to the proposed nearby supernova. New isotopic evidence has only added to the uncertainty felt by some investigators about where these processes occurred and how their products entered the presolar nebula. As one researcher puts it, "It's a very exciting field, but it's still very confusing."

Adding to the frustration, one of only two marble-sized chunks of meteorite that have yielded numerous anomalies has been almost completely consumed and searches for similar samples have failed so far. Of more immediate concern to researchers, Congress may drastically reduce the funding for the moon rock studies on which much isotopic anomaly work depends.

The game of fitting observed isotopic anomalies to astrophysical predictions of how anomalies might be created has become increasingly difficult, some would say impossible, as analysis of the available samples has become more thorough. Detailed analysis of several parts of the Allende meteorite by Gerald Wasserburg and his colleagues at the California Institute of Technology has shown that separate, apparently independent processes produced some of the isotopes. Also, Wasserburg's group believes that a connection between the isotopic evidence supporting the role of a supernova and some of the recently discovered anomalies has not yet been demonstrated.

The Allende meteorite has attracted so much attention in part because it was found to contain two 1-centimeter nuggets, or inclusions, that differed from numerous other inclusions only in their isotopic compositions (Fig. 1). It had been thought, after extensive searches, that wherever in the solar system a sample was collected, it would contain isotopes in the same proportions that are observed on the earth. The complete homogenization of the presolar nebula was supposed to take care of that.

Meteorites such as Allende, a carbonaceous chondrite, are considered to be the least altered samples of presolar material, and their inclusions probably represent some of the first material to condense from the presolar dust and gas. But even these have only grudgingly yielded anomalous isotopic patterns. The two tiny Allende inclusions are the only samples found so far that show a number of anomalies. The list of anomalies from all meteorite samples analyzed so far now includes, in addition to the first clear examples of oxygen and neon, the elements magnesium, silicon, calcium, barium, and strontium, the rare earth elements neodymium and samarium, and the inert gaseous elements helium, krypton, and xenon.

The case of magnesium illustrates the difficulties encountered recently in correlating the various anomalies. Magnesium of atomic weight 26 is the decay product of the relatively short-lived, radioactive isotope aluminum-26. If a meteorite sample is enriched in magnesium-26 with respect to its content of stable aluminum-27, it is assumed that newly synthesized, unstable aluminum-26 was present when the rock formed. The magnesium-26 provides a "fossil" record of a now vanished meteorite component. It is the only anomaly providing information on the timing of a supernova. Some individual mineral grains separated by the Caltech researchers from the less anomalous inclusion, designated C1, failed to show the high levels of magnesium-26 found by previous analyses. Other Allende inclusions, with no anomalies in calcium, strontium, or barium, do have a record of relatively high initial levels of radioactive aluminum-26. In contrast, inclusion C1 as a whole has a number of anomalous elements but little excess magnesium-26. All this variability has muddled the question of how aluminum-26, which is generally associated by theorists with a supernova, was mixed with other anomalous isotopes and eventually distributed among the mineral grains of meteorites.

Further complicating the game, the isotopic compositions of some of the heavier elements in the Allende inclusions indicate that there was more than one set of nucleosynthetic processes and that the separate processes were not necessarily linked to one another. The Caltech group and G. Lugmair and colleagues at the University of California at San Diego have analyzed the Allende inclusion having the larger and more numerous anomalies, inclusion EK 1-4-1. They found that the abundance patterns

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