CURRENT DEVELOPMENTS AND ISSUES: A SUMMARY

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REPRODUCTIVE ENGINEERING: IN VITRO FERTILIZATION

Young woman in IVF program develops ovarian cancer

A 25-year-old woman developed ovarian cancer after undergoing several superovulations on the IVF program at Southmead Hospital in Bristol, United Kingdom, report Marian E. Carter and David N. Joyce of Southmead's Department of Obstetrics and Gynaecology.

"Although hormones may not directly initiate tumor formation, they can act as promoters in the process of carcinogenesis," Carter and Joyce comment. "In the early stages, excessive hormone production may lead to hyperplasia of the target organs. The greater number of cells increases the probability of an initiating hit by some carcinogenic agent. Moreover, proliferating cells have a greater sensitivity to such initiation. In the later stages, some hormones have been shown to be important in the maintenance of tumor growth."

The young woman was admitted for laparoscopic oocyte collection in June 1984. She had had a course of norethisterone to control the previous menstrual cycle. Then an ovulation induction regime was begun. It included the administration of clomiphene citrate, Perganol, luteinizing hormone (LH), and human chorionic gonadotropin (hCG). At laparoscopy, five follicles were aspirated, yielding three mature eggs. Two embryos developed and were transferred, but the woman did not become pregnant.

A second attempt was made in September 1984. At laparoscopy, she was found to have ovulated. No eggs were retrieved.

There was a third attempt in August 1985. At laparoscopy, adhesions that appeared caseous (cheeselike) had developed in the abdomen. Only a small area of the right ovary was identifiable. No eggs were collected. Biopsies were taken from the left tube and fluid was aspirated from the pouch of Douglas and sent for cytological examination and culture.

Five days later the woman appeared at the clinic with lower abdominal pain and a firm, nontender, 14-week-size pelvic mass. Ultrasound revealed multiple cysts in both ovaries.

Three days later she was admitted because of continuing pain and discharged after six days.

The histology of the tubal biopsy showed papillary carcinoma. She was readmitted for laparotomy.

"At operation," the physicians wrote, "a partially necrotic tumor was found to fill the pelvis. It involved both ovaries, which were enlarged to a maximum diameter of 8 cm. Tumor covered the uterus and bladder." Physicians performed a subtotal hysterectomy, bilateral salpingooophorectomy, and omentectomy and removed the larger peritoneal tumor deposits.

The woman was given chemotherapy. Six months after the operation, Carter and Joyce write, she is well.

These physicians cite a paper suggesting that elevated gonadotropin levels are implicated in the development of ovarian tumors (D. W. Cramer and W. R. Welch, 1983, Determinants of ovarian cancer risk. II. Interferences regarding pathogenesis. *J. Natl. Cancer Inst.* 71:717–721).

Two previous cases of ovarian carcinoma have been reported in women having ovulation induction therapy, they note.

"The question raised by these cases is whether excessive gonadotropins played any part in the development of ovarian neoplasia," they write. Gonadotropins are used in IVF to multiply the number of available oocytes, they note.

They continue: "Puncture and aspiration of the follicles are believed to be responsible for the

avoidance of the clinical syndrome of ovarian hyperstimulation. In this patient, aspiration was not possible. As well as hyperstimulating normal ovarian tissue, the gonadotropins may have accelerated neoplastic growth. It is a matter of concern that in all three cases, the tumors developed with remarkable rapidity."

MARIAN E. CARTER and DAVID N. JOYCE, 1987, *Journal of in Vitro Fertilization and Embryo Transfer.* Ovarian carcinoma in a patient hyperstimulated by gonadotropin therapy for in vitro fertilization: A case report. 4(2): 126–128.

Can IVF cause infertility?

As Israel IVF center reports two cases in which physicians may have been responsible for damaging the previously healthy fallopian tubes of women. Tubal obliteration possibly occurred as a result of adhesions following IVF laparoscopy.

Physicians from the Harry and Abe Sherman Institute of Fertility, Golda Meir Medical Center in Petah Tikva, Israel write: "We report two patients in whom relaparoscopy for repeated ovum pickup revealed a large number of intrapelvic adhesions in the region of the adnexa, where the pelvis was clean of adhesions previously. We believe that these may have resulted from trauma to the ovaries and peritoneal surfaces, as well as bloody fluid resulting from punctures of the ovaries and possibly increased by flushings with heparin of follicular beds containing tiny, open blood vessels."

In one case, a 28-year-old woman was referred to the Institute because of six years of unexplained infertility. A hysterosalpingography and laparoscopy both revealed patent tubes and a clean intraperitoneal cavity without adhesions.

After superovulation, eight eggs were sucked out of her ovaries by means of 10 punctures to the ovaries. The woman did not conceive.

Six months later, she returned for another IVF go-round. When physicians performed a laparoscopy this time, they found multiple intraperitoneal adhesions around the internal genital organs. (In the interval between laparoscopies, there had been no events such as pelvic infection, the physicians emphasize in their report on this case. The implication is that the adhesions were a result of the previous IVF attempt.) Because of the multiple adhesions, egg suction was more difficult this second time. Five eggs were sucked out. The woman did not become pregnant.

In the second case, 10 eggs were aspirated from a 26-year-old woman after 11 punctures of the ovary. Laparoscopy proved that there were no adhesions in the intraperitoneal-pelvic cavity. The woman did not conceive after embryo transfer.

Six months later, physicians performed laparoscopy for a repeat IVF attempt. This time, the ovaries were covered with adhesions. Again, no intraperitoneal events each as pelvic infection had occurred between operations to account for the adhesions. Four eggs were sucked out. The woman did not conceive.

Physicians from the Sherman Institute of Fertility comment: "It is a well-documented fact that ovarian surgery … predisposes the patient to the development of multiple adhesions in the pelvis … In fact any surgical procedure involving the accumulation of blood-stained fluid in the intraperitoneal space involves the formation of postoperative adhesions … Other predisposing factors for the formation of adhesions, however, such as tissue trauma or manipulation resulting in tissue reaction or puncture of the ovaries or flushing of the follicular bed with medium added with heparin, obviously cannot be avoided during ovum pickup."

They note that when the only indication for IVF is *the male partner's infertility,* the impairment of the woman's fertility through physician action (iatrogenesis) may prevent the woman from conceiving spontaneously in the future with the same or possibly another husband.

"Furthermore," they add, "it is a well-known fact that a certain, although minimal, proportion of the couples waiting for IVF-ET, or following unsuccessful IVF-ET, conceives spontaneously. If an iatrogenic mechanical factor is superimposed unintentionally, we diminish their chances for spontaneous pregnancy."

ASHKENAZI, JACK, FELDBERG, DOV, BEN DAVID, MORDECHAI, SHELEF, MICHAL, DICKER, Dov, AND GOLDMAN, JACK A., 1987. Ovum pickup for in vitro fertilization: A cause of mechanical infertility? *J. Vitro Fertiization and Embryo Transfer* 4(4): 242–245.

IVF eggs show high levels of chromosomal

abnormalities

"Almost half the human eggs harvested in order to produce test-tube babies may be abnormal, if the findings of a Swedish study apply generally. Researchers do not know whether this high rate of abnormality is natural. It could be the result of fertility drugs that doctors give women to make their ovaries produce several mature eggs all at once. Hakan Wramsby of the University of Lund studied 23 eggs recovered from 17 women. The researchers developed a way of looking at the chromosomes of the eggs with less risk of damaging them accidentally. They found that half the eggs had either too few or too many chromosomes." They speculate that this may explain why in vitro fertilization is so unsuccessful. Other reports support their finding of a high frequency of chromosomally abnormal oocytes in clomiphene-stimulated cycles (R. H. Martin, M. M. Mahadedams, P. J. Taylor, K. Hildebrand, L. Long-Simpson, D. Peterson, J. Yamamoto, and J. Slephas, 1986. Chromosomal analysis of unfertilized human oocytes. *J. Reprod. Fertil.* 78: 673–678. M. Plachot et al. 1986. Chromosome investigations in early life. I. Human oocytes recovered in an IVF programme. *Hum. Reprod.* 1: 547–551. H. Wramsby and K. Fredga. 1987. *Hum. Reprod.* Chromosome analysis of human oocytes failing to cleave after insemination in vitro. 2: 137–142.)

H. WRAMSBY et al. 1987. Chromosome analysis of human oocytes recovered from preovulatory follicles in stimulated cycles. *New England Journal of Medicine.* 316: 121–124. *New Scientist.* 1987, January 29: 25. "Mutants hamper test-tube work."

Gene probe used to determine sex of human IVF embryos

"Two British medical teams have succeeded in identifying the sex and detecting hereditary diseases in newly fertilized embryos . . . The University of Edinburgh's in vitro fertilization team devised a test which uses a commercially available gene probe to identify the male Y chromosomes in embryos four to eight days old.

"Seven human embryos were investigated and six of these were positive for Y-chromosomes and thus were male. The Edinburgh team says the probe could be used to test embryos obtained during IVF treatment or normally fertilized embryos collected by uterine flushing, and could lead to prenatal diagnosis of sex–linked genetic diseases. Further research is necessary to perfect techniques to remove a single cell from the embryos, while using cryopreservation before implanting unaffected embryos into the mother's womb . . . "

Robert Winston and his IVF team at London's Hammersmith Hospital are also using gene probes to detect hereditary diseases in embryos.

"Winston says he will be ready to apply the animal-tested technique in humans in 'a matter of months.' … A service to detect genetic disorders and hereditary diseases such as cystic fibrosis, hemophilia, muscular dystrophy and Down's syndrome is expected to be offered by a new IVF clinic due to open at Hammersmith Hospital in October. These successes … have led to reports in British newspapers that parents will soon be able to choose the sex of their test-tube babies … Both teams deny that this is the intention.

"Dr. John West of the Edinburgh team says: 'It certainly wouldn't be ethical to use the method to choose the sex of a baby. But we couldn't prevent the technique being used that way.'"

KATHY JOHNSTON, 1987. Sex of new embryos known. *Nature.* 327: 547.

New methods for penetrating the egg

IVF researchers are experimenting with methods to increase the fertilization rate by injecting one sperm directly into the egg (microinjection) or by removing the zona pellucida, the egg's thick outer coat. The zona pellucida, which is made up of glycoproteins (proteins with sugar groups attached to them), is the first thing the sperm encounters in its attempts to fertilize the egg. The sperm head produces an enzyme that breaks down these proteins so that it can approach the egg's cell membrane. The sperm then fuses with the egg cell membrane, which causes changes to take place in that membrane that prevent other sperm from fusing. It is the zona pellucida that prevents sperm of another species from fertilizing an egg.

In their efforts to help sperm penetrate the egg, British IVF researchers Robert Edwards and Patrick Steptoe completely remove the zona pellucida. Other IVF researchers are skeptical of this method as the exposed egg could be fertilized

by many sperm. This causes the resulting embryo to die.

Leading Australian IVF researcher Alan Trounson is working on microinjection. The method involves helping sperm that cannot swim properly because they have twisted tails or abnormal heads. These sperm have difficulties passing through the zona pellucida. Trounson picks up one sperm in a tiny needle and injects it inside the egg.

Trials of the technique have achieved 75 percent "success rates" although they have yet to report a pregnancy.

P. WASSERMAN, 1987. The biology and chemistry of fertilization. *Science.* 235: 553–559. B. Dale, 1987. Mechanism of fertilization. *Nature.* 325: 762. S. Downie, 1986. A helping hand for deformed sperm. *New Scientist.* Dec. 11: 21.

Egg coat protein protects embryos

"Doctors at a London hospital have discovered . . . a glycoprotein which lines the walls of the fallopian tubes and also coats the egg and early embryo during its five-day journey down to the uterus. The doctors believe that the protein may play a crucial role in maintaining the embryo's viability so that it is more likely to form a healthy fetus."

The protein may act as a doorkeeper on the zona pellucida by regulating which substances are allowed to cross it. Or it may repel foreign objects that could damage the early embryo. It may also form a "shell" from which the embryo "hatches" when it is ready to implant into the wall of the uterus. If the protein is absent, as in test-tube embryos, the embryo may not be able to "hatch." The doctors plan to synthesize the protein and add it to the culture medium used to grow IVF embryos before transfer.

D. POWELL, 1987. Protein coat protects early embryos. *New Scientist.* March 19: 25.

Scientists' group issues guidelines on IVF

The Voluntary Licensing Authority (VLA), set up in Britain in 1985 by the Medical Research Council and the Royal College of Obstetricians and Gynaecologists, has issued new guidelines for in vitro fertilization. According to the guidelines, doctors should avoid introducing more than three embryos into a woman's womb at one time to avoid dangerous multiple pregnancies. Clinicians at some clinics regularly transfer four or more embryos and later may abort some of the fetuses selectively to reduce numbers. The VLA finds this practice "unacceptable."

The VLA also disapproves the use of eggs donated by an infertile woman's sister. Recently at Wellington Humana Hospital in London, three women gave birth to babies created from eggs donated by their sisters.

The VLA argues that the egg donators should remain anonymous "in the best interests of the child." The VLA also urges clinicians to shelve plans to use frozen eggs in in vitro fertilization until there is some assurance that the procedure is safe. Alan Trounson of the Melbourne IVF clinic has found that freezing can cause chromosome abnormalities. At least three babies have been born in Adelaide, Australia from once-frozen eggs.

GAIL VINES, 1987. New shackles hamper test-tube baby researchers. *New Scientist.* May 14: 22. Simon Hadlington, 1987. Embryo guidelines opposed by clinics. *Nature.* 327: 92.

Genetic diagnosis of embryos highlights Human Reproduction Conference

"Debates at the third annual meeting of the European Society of Human Reproduction and Embryology in Cambridge . . . centered around two issues: how many embryos . . . should be transferred" into the mother's womb after in vitro fertilization and "are we ready to begin testing embryos for genetic defects?"

Behind the debates lies the fear of a possible ban on human embryo research caused by negative public opinion. The Voluntary Licensing Authority (VLA) has ruled that no more than three embryos should be transferred at one time to minimize the danger that multiple pregnancies pose to both the mother and her fetuses.

"The same restrictions apply to . . . GIFT (gamete intrafallopian transfer) where eggs and sperm are transferred directly into a woman's fallopian tubes.

"Most clinicians working in the field … have modified their clinical practice accordingly. Ian Craft and his colleagues at the Humana Hospital in London, however, vehemently oppose it. Craft argues that his clinic's experience with GIFT shows that 85 percent of the pregnancies are

singletons and only one percent are quadruplets" even when 11 or more embryos are transferred.

But when a multiple pregnancy *does* occur, what can be done? Craft and his colleagues have performed "selective terminations," puncturing the hearts of one or more fetuses in the womb, killing them.

". . . Genetic tests for human embryos are imminent according to many scientists and clinicians at the meeting . . . Two breakthroughs in research on animal embryos . . . have convinced many . . . that they can now embark on 'preimplantation diagnosis' of genetic diseases."

Marilyn Monk of the Medical Research Council's Mammalian Development Unit in Britain created a strain of mice that lacked a certain enzyme and then correctly diagnosed those embryos carrying this defective gene. She managed to remove one cell of each embryo at the eight–cell stage and use it for a biochemical assay that determined the amount of enzyme present in the cell. The other seven cells of normal embryos were transferred to surrogate mice and most implanted.

Phil Summers of the Institute of Comparative Physiology in London has performed a similar operation on marmoset monkey embryos. He removed cells from eight-day-old embryos. These embryos contain 150 cells, some of which are destined to become the placenta. He cut away about one-third of the embryo cells (those that develop into part of the placenta) and cultured them. His biopsy contained enough cells to analyze the DNA. After biopsy, the embryos were transferred into female marmosets and six transfers resulted in pregnancy. Recently, the first birth occurred resulting in a normal-sized baby marmoset.

"These studies have . . . established . . . that we have the embryological techniques to sample human embryos without damaging them. Molecular geneticists also think they have nearly perfected ways of analyzing the DNA from just a few cells."

"'Has anyone biopsied human embryos?,' someone asked in Cambridge. Came the reply: 'Not yet, but soon.'"

GAIL VINES, 1987. New insights into early embryos. *New Scientist.* July 9: 22–23.

The Catholic Church rules on IVF

The Vatican has released its document on IVF, "Instruction on Respect for Human Life and its Origin and on the Dignity of Procreation." The report condemns IVF, the abortion of severely abnormal fetuses, and research on embryos as immoral. On IVF it states that "such fertilization entrusts the life and identity of the embryo into the power of doctors and biologists and establishes the domination of technology over the origin and destiny of the human person."

However, there are some loopholes for Catholic couples.

"If the technical means facilitates the conjugal act or helps it to reach its natural objectives, it can be morally acceptable."

Treatments that involve fertilization inside the body and do not obtain sperm by masturbation are thus acceptable. One such method is gamete intrafallopian transfer (GIFT) where doctors extract a woman's egg from the ovary, place it in a plastic tube with sperm and inject it directly into the fallopian tube. The sperm can be collected in a condom worn during intercourse provided that the condom is perforated to allow the possibility of natural fertilization.

An editorial in *Nature* criticized the document: "The Vatican has done itself more harm than good with its statement last week on the lawful and illicit use of new techniques in human embryology … If taken at its face value it could be a drag on research and the therapeutic techniques that will follow."

GAIL VINES, 1987. Perforated condom offers loophole in papal rules on IVF. *New Scientist.* March 19: 19. *Nature.* 1987. The Vatican and embryology. 326: 229. Constance Holden, 1987. The Vatican weighs in. *Science.* 235: 1455.

A SCIENTIST'S DISSENT

Molecular biologist opposes reproductive technologies

In the journal *Nature,* molecular biologist Erwin Chargaff has stated his reasons for opposing reproductive technologies. "It is often said that progress … is driven by technology. An alternative view can also be heard: that requirements, demands, urges arising in an unexplained manner, generate the techniques suitable for satisfying them

… The semiindustrial production of babies seems to belong to the first category: the demand was less overwhelming than the desire on the part of the scientists to test their newly developed techniques. The experimental babies produced were more of a by-product … To all of us grown up in an atmosphere of freedom of thought and expression, it seems unthinkable that there can be excesses of scientific research. Reproductive technology…. appears to represent one such example … Helping a few couples condemned to childlessness towards getting a child may strike the obstetrical cytologist as such a laudable step. But we can already see the beginning of human husbandry, of industrial breeding factories. And who can hinder the mass production and industrial exploitation of human embryos, the emergence of a new branch of biotechnology?

"… I see only two ways of preventing even worse from happening, and that is to moderate two human traits, cupidity and ambition. If the money nexus were cut so that all that now makes up reproductive technology would have to be performed without compensation, as truly Samaritan deeds, if anonymity were enforced, so that all the remarkable achievements of the new applied science would have to be published without authors' names almost all regrettable excesses would be avoided."

ERWIN CHARGAFF, 1987. Engineering a molecular nightmare. *Nature.* 327: 199–200.

PREVENTABLE INFANT DEATHS

Newborns' weight linked to mother's social status in Sweden

A recent study in Goteborg, Sweden, has shown that babies born to women with low education and low income are more likely to be underweight and less healthy than those born to women with higher education and better incomes. There may also be a link between birth weight and how near the mother lives to a factory that produces air pollution.

PETER SANDBERG, 1987. Utslapp kan ge fosterskador. *Dagens Nyheter.* January 13.

Malnutrition leads to underweight babies in Britain

"Women at risk of giving birth to underweight babies are suffering from malnutrition according to a study in London … Underweight babies are more likely to die soon after birth and to suffer nongenetic forms of handicap. The researchers discovered that the mothers of underweight babies consumed only an average of 1304 calories a day in the first three months of pregnancy, 1000 calories fewer than recommended by the Department of Health."

The group studied ate more than the recommended 60 grams of protein a day but ate significantly fewer fatty acids. Researchers suspect "that the fatty acids are needed especially in early pregnancy to build a healthy placenta with a rich supply of blood vessels."

Almost half of the women with underweight babies were unemployed. As the researchers conclude: "They may not attach a high priority to their choice of food when they have more pressing problems."

GAIL VINES, 1986, December 25. Takeaway diet leads to underweight babies. *New Scientist.* December 25: 22.

Mortality in black infants is twice that in whites in North America

In 1984, first-year infant mortality for blacks was about 18 deaths per 1000 births, in contrast to 9 deaths per 1000 births for whites, according to data from the National Center for Health Statistics.

It is not simply that mortality in black infants is twice the rate for whites in North America, the Centers for Disease Control in Atlanta, Georgia report. Black infants also have a higher chance than whites of being born at a low weight (under five and a half pounds). Even those with a higher birth weight have a smaller chance than whites of surviving their first year.

If black infants had had the same average birth weight and mortality as white infants in 1980–the lastest year surveyed in depth – 5526 fewer black infants would have died, the Centers for Disease Control report. The deaths of these black infants were preventable.

Ob. Gyn. News, 1987. Mortality in American black infants is twice that seen in whites. 22(6): 38.

EMBRYO EXPERIMENTATION

Editorial on British 1VF rules

The journal *Nature* has published an editorial on IVF regulations. "What (if anything) should be done to regulate research and medical practice in human embryology? … In most places, most of the USA for example, laissez faire seems to be the guiding principle. Elsewhere, as in Australia, there are islands of zealousness (the state of Victoria) in a sea of relative indifference. In West Germany, it seems that the cards are being dealt for what will be a battle between the federal justice ministry and professional interests, while in Britain, where the government three years ago welcomed the report of its Warnock committee, promised legislationis still not forthcoming … The oddly named Voluntary Licensing Authority … is complaining that both its own work and research in human embryology are being hampered by he continuing lack of legislation … The betting is that a bill will not appear until October 1988."

Nature, 1987. IVF remains in legal limbo. 327: 87.

Embryo experimentation law in Federal Republic of Germany opposed

In April 1986, a law was drafted in the Federal Republic of Germany that would make it a criminal offense to conduct research on human embryos and to genetically manipulate human germ-line cells (sperm and eggs). Justice Minister Hans Englehard is trying to push the law through Parliament. The two principal West German research organizations – Deutsche Forschungsgemeinschaft and the Max-Planck-Gesellschaft – have issued position papers in response to the proposed law. The two organizations "want to keep jurisdiction over embryo research under the control of doctors and scientists." The Max-Planck-Gesellschaft paper expresses fear that "the introduction of criminal penalties will frighten scientists away from potentially valuable research."

The Deutsche Forschungsgemeinschaft paper stated "that one cannot discount the possibility that such research might continue anyway despite the harsh penalties. [It] criticized the irresponsibility of forbidding research in West Germany that will probably be done elsewhere … It would be 'almost immoral' to let another country do the research and then use the results."

The two organizations also "point but that, to them, the proposed law is inconsistent with West Germany's liberal abortion law. 'It seems inconsistent to researchers,' says Deutsche Forschungsgemeinschaft president Hubert Markl, that 100,000 abortions are performed each year but that the law 'forbids the use of an embryo in a research experiment.'"

STEVEN DICKMAN, 1987. West German research agencies oppose new embryo law. *Nature* 327: 6.

Conflicts over definition of embryo in Australia

"What is an embryo? The answer could provide a solution to some of the issues raised by the Infertility Medical Procedures Act which came into effect in August 1986 in the state of Victoria." This law "prompted Alan Trounson, leader of Monash University's … IVF team to issue an ultimatum that he and his team would go overseas within six months if they were not allowed to continue research."

The legislation forbids the destruction of embryos but it does not define either "embryo" or "fertilization." One definition being discussed is this: An embryo exists 20 hours after fertilization when the male and female genetic material fuse together. Another definition: An embryo exists 14 days after fertilization.

The Monash team has requested the Standing Review and Advisory Committee on Infertility to issue a clarification of the terms used in the legislation. If the 20–hour limit on embryo experimentation were adopted, this would allow approval of two proposal experiments. That would be enough to ensure that the Monash team stays.

The Monash team would like to see the adoption of the term "pre-embryo" for the initial 14-day period. ["Pre-embryo" is a term invented and introduced in 1986 in Britain by the Voluntary Licensing Authority, an organization founded by two groups of physicians and researchers.]

CHARLES MORGAN, 1987. New Australian law on embryos still confuses researchers. *Nature.* 325: 185.

FETAL TISSUE

Fetal brain cell transplants

Two Swedish research groups, one at Karolinska Institute in Stockholm and the other at the University Hospital at Lund, have succeeded in transplanting human fetal brain cells into damaged rat brains. The cells grew and built new nerves in the damaged area, causing relief of the symptoms of a Parkinson's-like disease in the rats. The cells were taken from aborted fetuses obtained after routine abortions at the hospitals. New ethical guidelines allowing the use of aborted fetuses for research purposes came out last year. The ultimate goal of this research is to perform similar transplants on patients with Parkinson's disease.

LENNART EDQVIST, 1986. Celler fran foster transplanteras and Godtagbart anvanda foster for forskning. *Sydsvenska Dagbladet.* December 1: 10.

Huntington's chorea treated with fetal brain cell transplants

Researchers at Lund's University have succeeded in transplanting fetal rat brain cells into adult rats with Huntington-like symptoms. The symptoms of the disease disappeared and studies of the rat brains snowed that the fetal cells had reestablished contact within parts of the brain that had been damaged. Similar research has been done on Parkinson's disease using human fetal cells in rats.

ANDERS OLSSON, 1987. Lyckad tansplantation av friska hjarnceller *Sydsvenska Dagbladet.* May 14. Ole Isacson, 1987. Neural grafting in an animal model of Huntington's disease. Ph.D. dissertation. Histology Institute. University of Lund, Sweden.

BIRTH REGULATION

Romania's "birth squads"

Romania's leader, Nicolae Ceausescu, has created "birth squads" consisting of Communist Party functionaries and police agents. "They visit married women at home and ask detailed questions about their private life and why their sexual activity is not leading to conception." The squads are the latest effort to increase the birth rate and cut the abortion rate in Romania.

The campaign to increase the birth rate began in 1984 when a directive came that all women "of child-bearing age [must] undergo a monthly medical exam at work. If the test indicates a pregnancy, then failure to produce a child within nine months can result in charges being brought against the woman."

The campaign includes financial penalties for those who fail to breed. Adults who are not married at 25 must pay extra taxes and there are tax penalties for childless couples who cannot provide a medical reason for not having children.

Ceausescu explains his crusade: "The fetus is the socialist property of the entire society. Giving birth is a patriotic duty which is decisive for the fate of the country. Those who refuse to have children are deserters, fleeing from the laws of our national continuity."

New Scientist, 1986…as Romania presses for procreation. December 25: 8.

Troubles with contraceptive implants

Contraceptive implants were introduced in Sweden in 1965. Six small rods containing gestagen, a hormone, are placed just under the skin of the upper arm. Clinical tests at the Academic Hospital in Uppsala recorded few side effects. But at other hospitals and clinics, women have shown hemorrhaging and other effects that can be blamed directly on the implants. In several cases, the implants couldn't be found when they were to be removed. KabiVitrum, the manufacturer of the implant [known as Norplant] is now contacting gynecologists, instructing them in how to implant the contraceptive properly. In some cases the rods have probably been placed too deeply under the skin, where they can then wander to other part of the body. The women who have had problems have organized themselves and hired a lawyer. They want KabiVitrum to take the implant off the market until it has been improved. They suspect that the level of gestagen in the implants is much too high.

MARIANNE HEDENBRO, 1987. Larm till lakare om p–stavarna. *Sydsvenska Dagblandet.* May 13.

SEX DETERMINATION

Science helps eliminate baby girls in India

"Most of Bombay's private gynecologists are

performing … [amniocentesis] to determine the sex of the fetuses. If it is a girl, many doctors perform abortions."

Amniocentesis is done around the 18th week of pregnancy or later. It involves removing some of the fluid around the fetus and checking the fetal cells floating in it for genetic defects. The method also reveals the fetal sex and is establishing a new practice: killing female fetuses. This substitutes for the old practice of female infanticide.

"The extent … of female feticide is outlined in a survey, *Sex Determination Tests and Female Feticide in Greater Bombay* … This survey may prove embarassing for the state government, which has been deferring legislation to prevent female feticide, saying the practice is not widespread." Fifty doctors were interviewed in the report and "42 admitted to performing a total of 269 tests per month … If the doctors are typical of others in Bombay, then at least 16,000 tests are carried out each year,… [meaning] 8000 female feticides in Bombay alone."

A third of the doctors "said that in some cases the women's husband or in–laws had forced her to undergo the test …. For decades, the proportion of baby girls registered in India has been declining, partly as a result of female infanticide … Feticide is likely to unbalance the ratio further."

Sex determination "is also being incorporated into the dowry system. The government banned dowries several years ago, but the practice of families offering money or goods in return for a man marrying a daughter continues … Instead of breaking with the dowry system, couples attempt to ensure that their child is a recipient of a dowry (a male), not a donor."

New Scientist, 1986. "India makes sure of baby boys." December 25: 8

Gynicide in Britain

"Some pregnant women in Britain are seeking abortions when told the sex of their fetus, doctors have alleged. As a result, some laboratories that test for fetal abnormalities are withholding information about the sex of the fetus from patients. One laboratory that has stopped routinely reporting sex is the Kennedy Galton Centre in Harpenden." The Centre's Michael Ridler "says that evidence has accumulated … of women who seek abortions when told the sex" [of their fetus]. "The centre will now … only disclose the sex if obstetricians specifically request it. Similar restrictions are in operation elsewhere" such as Watford General Hospital and in the West Midlands region.

"Michael House, who performs the tests at West London Hospital, believes it is unethical for doctors not to tell patients the results of tests."

"… A number of obstetricians said privately that the problem was most serious among Muslim families where there is strong pressure to have boys. Some felt … that in certain cases such cultural pressure could endanger the mental health of the mother if, say, she already had three or four girls. In such cases, the mental stress that could result from having another girl would provide grounds for abortion." Many think that now that simpler prenatal tests are available, the problem may get worse. One such test is chorionic villus biopsy, which can be carried out at nine weeks of pregnancy.

M. HULTEN et al., 1987. Preventing feticide. *Nature.* 325: 190. Pereva, Judith. 1987. Sex seals the fate of fetuses in Britain. *New Scientist.* January 22: 22.

Ethics debate on releasing information on fetal sex

A report from India over the increase in female feticide after amniocentesis has provoked a debate within Britain's medical profession over the ethics of withholding information from patients. British cytogeneticists have begun withholding information on fetal sex obtained from amniocentesis.

"The debate has been reopened by the Association of Clinical Cytogeneticists, which has become increasingly concerned over the potential misuse of amniocentesis data … Health authorities have become increasingly concerned that the problems of India may be repeated in Britain, particularly among certain ethnic groups."

BILL JOHNSTONE, 1987. Britain's doctors in legal wrangle over confidentiality of records. *Nature.* 325: 567.

GENETIC ENGINEERING: AGRICULTURAL USES

Activists vandalize first field tests of ice minus

bacteria

Researchers at Advanced Genetic Sciences Inc. of Oakland, California, finally received permission to spray a strawberry patch with genetically altered bacteria – so-called "ice-minus" bacteria. Within 24 hours of the decision, activists managed to slip past two security guards at the test site where they uprooted 80 percent of the plants. Advanced Genetic Sciences replanted the strawberry patch but many of the blossoms were destroyed. This means some of the experiments will be delayed.

Advanced Genetic Sciences then sprayed the plants with its bacteria, "Frostban," on April 24. This is the first deliberate release of genetically engineered bacteria sanctioned by the Environmental Protection Agency (EPA). Advanced Genetic Sciences had previously had its permit suspended by EPA because it conducted unauthorized outdoor tests of the bacteria.

On May 25, the same thing happened to researcher Stephen Lindow near Tulelake in northern California. Activists from Earth First!, an environmental group, claimed responsibility for uprooting 4,000 potato plants that were about to be sprayed with a similar genetically engineered bacteria developed by Lindow. The potato plants were replanted and spraying went ahead as scheduled.

MARK CRAWFORD, *Science.* 1987. California field test goes forward. 236: 511. M. C, 1987. Vandals hit Lindow plot. *Science.* 236: 1181. Marcia Barinaga, 1987. Field test of ice-minus bacteria goes ahead despite vandals. *Nature.* 326: 819. Ian Anderson, 1987. Activists savage outdoor gene test plot. *New Scientist.* June 4: 32.

Recombinant DNA guidelines to be relaxed in USA

"A series of changes to simplify regulations governing the conduct of laboratory research, field experiments and industrial operations involving genetically engineered organisms has been adopted by the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health in the USA."

The changes apply only to research funded by NIH.

"The committee recommended that in most cases, experiments and field tests that are approved by another federal agency need not be reviewed by the Committee. For example, Steven Lindow's proposal to test [ice–minus bacteria] on potatoes … would only require approval from the Environmental Protection Agency."

The committee recommends that organisms engineered by deleting a gene "be exempted entirely from regulation … Rearrangements and changes within a [species] … should also be exempt."

MARK CRAWFORD, 1987 RAC recommends easing some recombinant DNA guidelines. *Science.* 235: 740–741.

Committee recommends law on release of genetically altered organisms

The British government should consider legislation to control the release of genetically engineered organisms into the environment, according to a recent report by the House of Lords Select Committee on the European Communities.

Now, scientists are merely asked to abide by voluntary rather than statutory guidelines. The Committee writes that the European Community's programs of biotechnology research "pay insufficient attention to environmental aspects."

New Scientist, 1987. Lords call for laws to govern release of gene-spliced organisms. June 25: 33.

U. S. vaccines to be tested in India

"India will become the testing ground for several new vaccines being developed in the USA following an Indo-US agreement on a Vaccine Action Program."

The agreement "has paved the way for trying out in India advanced and genetically engineered vaccines that might, for practical reasons, be difficult to test in the USA.

"India has always been sensitive to its people being used as guinea pigs in trials of drugs vaccines developed elsewhere … This difficulty has apparently been overcome by the USA which has associated Indian scientists with the US laboratories where the vaccines are being developed … By projecting the vaccines as products of Indo-US collaboration, the USA hopes to avoid opposition to clinical trials in India.

"Among the vaccines to be tested are those against diarrheal diseases [such as cholera, oral

typhoid vaccine] … and a recombinant DNA vaccine against hepatitis-B. The collaboration also provides for the testing of the vaccinia rabies recombinant vaccine developed at the Wistar Institute and used in a controversial experiment on cattle in Argentina … This has raised eyebrows among a section of the medical community.

"Dr. A. S. Paintal, director general of the Indian Council of Medical Research … said he would not allow any vaccine to be used in India unless it was also approved for use in the US by the Food and Drug Administration."

K. S. JAYARAMAN, 1987. Vaccines developed in United States to be tested in India. *Nature.* 328: 287.

GENETIC ENGINEERING: HUMAN APPLICATIONS

Cystic fibrosis gene localized

"Molecular biologists in London [England] have now identified a region of chromosome 7 that carries the gene for cystic fibrosis. They may have found the gene itself."

The researchers used a new technique for locating the gene marker. Molecular analyses of children with cystic fibrosis will soon determine whether they have found the gene itself. It will then become possible to diagnose carriers of the defect.

PETER GOODFELLOW, 1987. Classical and reverse genetics. *Nature.* 326: 824. *New Scientist,* 1987. Gene for cystic fibrosis. May 14:35.

Increase in use of DNA Probes

"Scientists first cloned a human gene in 1977. In the following year, geneticists first probed the DNA of a fetus to diagnose a genetic disease (sickle cell anemia)." This research has increased dramatically and researchers have studied more than 90 human diseases at the gene level.

New Scientist, 1987. Will clones take over the world? February 12: 32.

Animals can now be patented

As of April 3, 1987, the U.S. Patent and Trademark Office accepts patents for genetically altered higher animals. It calls Current Developments and Issues the animals "non-naturally occurring non-human multicellular living organisms".

This policy emerges from a case brought by the University of Washington over a genetically manipulated oyster. The appeals board of the Patent Office has referred to the Supreme Court ruling in 1980 on the patentability of genetically engineered microbes. It was the intent of the law, the appeals board ruled, that "everything under the sun made by man" could be patented.

There are currently 15 applications for animal patents. Hybrids and cross–breeds made by standard breeding techniques will not be eligible. Applicants must prove that the animal is manufactured and thus not found in nature.

Opposition to the decision is strong. The Humane Society has joined numerous other animal and farming groups in condemning the new policy. Critics state "that granting patents for higher life forms implies that [people] can create and claim ownership for new living things … The Foundation on Economic Trends has formed a coalition to attempt to have the patent office's decision rescinded."

These protests have spurred Congress to take action. Senator Mark Hatfield has asked the patent office not to issue any patents on higher life forms. He is drafting legislation that would rescind the Patent Office decision.

CAROL EZZELL, 1987, April 23. "Animals can now be patented." *Nature.* 312: 729. Christopher Joyce, 1987. Patent law protects altered organisms. *New Scientist.* April 30: 27. M. C. 1987. Congress to weigh animal patents. *Science.* 236: 1058.

The race to map the human genome has begun

A project to map the entire human genetic blueprint has quietly begun in three laboratories in the USA. It could become the largest single project in the history of biology.

Enthusiasm for embarking on a full scale sequencing effort is waning in favor of the more modest short-term goal of genetic and physical mapping of the genome. The U.S. Department of Energy has set aside US$5 million to map three chromosomes, starting immediately. Within five years, the Department hopes to have a rough physical outline of 24 different human chromosomes.

The final goal is to sequence the genome – a complete accounting for all three billion pairs of

chemical bases in the DNA that together make up all the human genetic material. The task may take several decades.

The Department of Energy is backing researchers at Columbia University, Los Alamos National Laboratory and Lawrence Livermore. (The latter two are military laboratories.) The three research centers will create physical maps of chromosomes 16 (Los Alamos), 19 (Livermore), and 21 (Columbia). The National Science Foundation will also help by supporting research at California Institute of Technology on a sequencing machine invented by Leroy Hood.

In England, Sydney Brenner, director of the Medical Research Council's Molecular Genetics Unit in Cambridge, is recruiting a team of 6 to 12 people to carry out a mapping project. Brenner has recently sequenced the genome of a nematode. The human genome is 50 times bigger than the nematode's. At the moment he plans to produce a physical map which he estimates would take 100 person-years (20 people working 5 years, for example).

At a recent meeting, the Department of Energy's Health and Environmental Research Advisory Committee approved a draft report urging that US$1,000 million should be spent over the next seven years on the Human Genome Project. Besides mapping chromosomes, the Department will work on developing new sequencing technologies and new means for handling the data.

The big question: Is knowing the genome's sequence worth the cost of US$300,000 to $3 billion? Many researchers oppose the giant program. David Botstein of the Massachusetts Institute of Technology says: "I do not believe that there is a strong scientific justification for knowing the sequence of the entire human genome. The motivation for doing it is frankly political, or 'science' political, more than it is that science is being held up by our lack of knowledge of every nucleotide (base pair) in the genome."

CHRISTOPHER JOYCE, 1987. The race to map the human genome. *New Scientist.* March 5: 35–39. David Swinbanks, 1987. Interest in the human genome project reaches new heights. *Nature.* 325:651. John Maddox, 1987. Brenner homes in on the human genome. *Nature.* 326: 119. Joseph Palca, 1987. Human genome sequencing plan wins unanimous approval in US. *Nature.* 326: 429. Roger Lewin, 1987. National Academy looks at human genome project, sees progress. *Science.* 235: 747–748.

Private company plans to map human genome

While federal agencies debate the merits of the genome project, a private corporation founded by Walter Gilbert of Harvard University has set out to beat everyone to the punch. Gilbert says his Genome Corporation will work out a map of the human genome for sale to anyone who may want it. The corporation will also sequence segments of the genome and market a database containing that information. His anticipated customers include the academic research community and the pharmaceutical industry.

JOSEPH PALCA, 1987. Human genome sequencing plan wins unanimous approval in US. *Nature.* 326: 429. Roger Lewin, 1987. Politics of the genome. *Science.* 235: 1453.

Japan developing human genome sequencing technology

Japan's Science and Technology Agency is setting up a program for sequencing the human genome. In collaboration with Seiko and Fuji Film, the agency has for several years been developing an automatic DNA-sequencing machine. Professor Akiyoshi Wada of Tokyo University has been leading the project. Sequencing DNA is a tedious, boring and time-consuming job. Researchers have been trying to develop automated sequencers that could take over this part of the work.

Seiko (which makes watches) was asked by Wada to build a prototype sequencer. Last year, a commercial version went on sale. Turn it on before going home and the machine will have up to 32 samples ready for the next step in the morning.

This next step in sequencing, separation by electrophoresis, is also a problem. The special gel sheets used can take half a day to make. So Wada asked Fuji Film to develop a system to mass produce gel sheets. In response, the company built a production line that can turn out 1,000 sheets a day. They went on the market in September 1986.

Now there are plans to try to automate the entire process. This would include connecting the sequencer to giant electrophoresis machines. Wada estimates that the system could sequence 300 million base pairs per year. He plans to

demonstrate the system's ability by sequencing one human chromosome. This would take 160 days and cost only US$11 million. The whole human genome would take 30 years and cost $600 million.

"In the 21st century, we forsee that DNA-sequencing supercenters will be set up in several countries," says Wada. Such centers would be biology's equivalent of "large particle accelerators and far-reaching programs of space research."

Science published an editorial recently on the need to sequence the human genome: "They [human subjects] offer a wealth of information in regard to basic biology that is not duplicated by any other species. Hereditary defects may be able to be diagnosed more efficiently and eventually eliminated."

BOB JOHNSTONE, 1987. Genes on the production line. *New Scientist.* March 5: 39–40. Akiyoshi Wada, 1987. Automated highspeed DNA sequencing. *Nature.* 325: 771–772. David Swinbanks, 1987. Japanese plans to sequence the human genome. *Nature.* 326: 323. Roger Lewin, 1987. Japanese super-sequencer poised to roll. *Science.* 326: 31. Daniel Koshland, 1987. Sequencing the human genome. *Science.* 236: 505.

Editorial on human genome project

"The answer to the question of whether the human genome should be sequenced is not so obvious … The notion that 'it is time to start running' along the chromosome sounds much like other clarion calls for a headlong rush into technological advances for which little or no political, legal, regulatory or even ethical preparation has been made.

"Nuclear technology was clearly introduced before the world was ready to deal with its consequences and such may be the case of sequencing the human genome. In view of our poor record in nuclear physics, is there any reason to suppose we will have any better success with the uses to which detailed knowledge of the human genome will be put?

CLEMENT COUNTS, 1987. Human genome sequencing. *Science.* 236: 1613.

Change in drug rule may help biotech firms

"Drug companies may soon be able to sell, rather than provide free of charge, experimental drugs to treat serious or life-threatening diseases before US Food and Drug Administration approval … This is one of the most controversial changes to the Investigational New Drug (IND) regulations" ever proposed. The "changes would permit a pharmaceutical company to charge for drugs administered to patients participating in clinical trials" so as to begin recovering the costs of developing the drug. The new regulation may "impose a financial burden on [patients] as most … health insurance companies will not pay for drug therapy not approved by the FDA …The new ruling would have a favorable effect on the biotechnology industry … as the development of drugs using genetic engineering is especially costly."

Nature, 1987, April 9. US experimental drug rule change may help biotechnology, p. 536.

West German report on genetic engineering

A report of a West German parliamentary commission, "Chances and Risks of Genetic Engineering," contains recommendations on the applications of genetic engineering. The commission generally approves the use and exploitation of genetic manipulation. However, it does call for a ban on experiments on fertilized human eggs that have the potential to develop into human individuals. It also calls for a five–year moratorium on the environmental release of genetically transformed microorganisms. The only person voting against the report was the representative of the Greens.

The report recommends the "promotion of the use of transgenic animals in biomedical basic research." The report welcomes more reliable and precise prenatal diagnosis by means of genetic techniques but states that there should be a guarantee that no unacceptable abortion practices will emerge. Experiments on human germ-line (eggs and sperm) are to be prohibited even if they are aimed at therapy "if the cells can grow into complete human individuals."

JURGEN NEFFE, 1987. West German commission reports on genetic engineering. *Nature.* 325: 474. David Dickson, 1987. German moratorium urged. *Science.* 235: 741.

Genetic engineering and biological warfare

"In 1972, the Biological and Toxin Weapons Convention was hailed as a model agreement and many countries agreed to ban biological weapons … Now there is a real possibility that biotechnology will bring a new generation of weapons not covered by the terms of the 1972 convention … The US Department of Defense plans to spend 150 million US dollars on chemical and biological weapons systems including a range of programs" based on genetic engineering. The Defense Department publishes lists of its research grants and contracts but the British Ministry of Defence refuses to do so.

"New research falls into three broad areas. The first lies in developing the existing range of chemical weapons [such as nerve gases]. The second area … is to produce existing toxins on a large scale or to engineer new ones … The third category … is work on infectious or potentially infectious organisms." Such organisms could be made more lethal or could be engineered to cripple another country's agriculture.

STEVEN ROSE, 1987. Biotechnology at war. *New Scientist.* March 19: 33–37.

U.S. Department of Defense must assess biological weapons' risks

"The Department of Defense must prepare an environmental impact statement covering research activities on biological warfare being conducted at 127 government, university, foundation and corporate laboratories in the U.S. The Department agreed to conduct the study as part of a court-supervised settlement" of a lawsuit brought by the Foundation on Economic Trends, a public interest advocate. "At issue was the department's failure to assess the potential environmental and human health effects of an accidental or deliberate release of pathogenic organisms …

"The Department of Defense is applying recombinant DNA techniques in research and the production of a range of pathogens and toxins including botulism, anthrax and yellow fever. This research has increased dramatically in the past five years, [the Foundation says] but the Department of Defense has failed to show that they have examined the health effects of these activities … As part of the court agreement, the Department of Defense is expected to evaluate evacuation, quarantine and medical treatment capacity … where there is ongoing defense research on biological warfare."

MARK CRAWFORD, 1987. DOD to reassess bioweapons risks. *Science.* 235: 968.

Cancer an occupational hazard in genetic engineering?

The assumption that work with genetically engineered products presents no danger can no longer go unchallenged. In June 1986, the press reported that five molecular biologists working with tumor viruses, oncogenes, and mutagens at the Pasteur Institute in France had contracted cancer (mostly bone cancer) at the same time.

Two of the scientists, Francoise Kelly and Yves Malpieve, have already died. "The others are seriously ill. All five worked in two adjacent laboratories on the same floor of one building." The Social Security Agency in France ruled that Malpieve's death was caused by an occupational disease.

The probability of such a cluster of cancer cases occurring is extremely remote. In June 1987, a sixth researcher who has worked with genetic engineering at the Pasteur has also contracted cancer. Preliminary investigations found that the work conditions in the labs were not sloppy nor were materials handled in any extraordinary way.

Oncogenes are part of an exciting area of research. Worldwide, hundreds of labs and thousands of researchers are doing research using oncogene material. Industry is now moving rapidly into this field. There is a substantial workforce at risk.

The problem seems to lie in the change of methods of working with oncogenes. Earlier research used precancerous mouse cells that were easily transformed to cancer cells by treatment with oncogenes. However, it was soon discovered that normal animal cells could also be induced to become cancerous when treated.

Recently, it has been shown that normal human cells grown in culture can also be made cancerous when treated with oncogenes. The same type of cells occur in the bodies of laboratory workers. There is little to stop the oncogenic agents from entering the bodies of lab workers, turning them into cancer victims.

The use of new cloning vectors based on the

bacteria *E. coli* (normally found in the intestines) also increases the risks. Previously, vectors were used that could not survive if they entered the human body. New vectors have been developed that have never been tested for this. "It seems inevitable that *E. coli* designed to produce oncogene proteins will enter the gut of lab workers. There the new cloning vectors could establish themselves … The gut would then act as a mini–factory, continuously producing the oncogene proteins" which have been shown to turn normal human cells cancerous. There are no regulations pertaining to the manipulation of oncogene DNA in the laboratory or in industry.

New Scientist, 1987. Cancer at the Pasteur. June 18: 29. Ditta Bartels, 1987. Escape of the cancer genes? July 30: 52–54.

Genetic diagnosis seen as the big market for biotech firms

"A gene carries the instructions that enable cells to make a particular protein … If the gene is abnormal, the protein is absent or malfunctioning. [Before, doctors] could diagnose genetic disease … only by looking for the biochemical consequences of the defective gene … Molecular biology has changed all that.

"Researchers now have the tools to directly identify defective genes."

For instance, the DNA of a fetus just a few weeks old can be analyzed for hereditary diseases such as sickle cell anemia and thalassemia.

"Research is also uncovering genes that influence a person's susceptibility to major killers such as heart disease and cancer. The ability to screen adults or children for such genes may well change the face of medicine.

"As researchers uncover more and more of the genes behind such 'multigene' disorders as heart disease, their ability to predict today who will die in 20 years time increases. The result of all this research is a new branch of commercial biotechnology. DNA tests are fast becoming a commodity traded in the medical market, much like pregnancy tests or insulin. The DNA itself is often a commercial secret. With new value has come more secrecy among researchers in molecular genetics, which worries academics. As usual, profit has pushed practice well ahead of ethicists and legislators, who have just begun to ask the questions: who owns human DNA? Can it be patented? How should people be counselled before they are told their future?"

CHRISTOPHER JOYCE, 1987. Genes reach the medical market. *New Scientist.* July 16: 45.