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2003 Erasmus Lecture

Sex and reproduction: ready for divorce?

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The effective separation of sex ('in bed') and fertilization ('under the microscope') has already been practised successfully for the past 25 years by well over one million people – virtually all of them suffering from infertility problems. But why, where and when will fertile people resort to assisted reproductive techniques to become parents? And why are the prospects for fundamentally new methods of birth control so dim?

Introduction

The question, 'What makes us human?' will never receive a black-and-white answer. It is the ideal sort of leitmotif for a convocation of intellectuals, typified by the Academia Europaea, since it will permit each speaker to ride a favourite hobbyhorse. I still recall a tentative answer advanced by a distinguished physician-writer-philosopher, the late Lewis Thomas.¹ 'If you are looking about for really profound mysteries, essential aspects of our existence for which neither the sciences nor the humanities can provide any sort of explanation, I suggest starting with music.' Instead of 'music,' one could, of course, proffer 'art' or 'humour' or 'wanton cruelty' among many other alternatives. Mine will be 'sex'.

I base my answer on the observation that humans are the sexiest of all species on earth. Among the millions of species, only we have sex for fun. Only we – and perhaps a couple of others such as the Pygmy Chimp (Bonobo) – are able and willing to have sex 365 days of the year. In all other species, copulation is seasonally controlled, and directly related to the optimal time for fertilization and the rearing of offspring. To have sex purely for love, lust or fun, but without reproductive consequences, requires the practice or at least aspiration to some sort of birth control. This could lead me to a second micro-definition of humanness:

‘deliberate birth control’. Of course, we also have sex in order to reproduce. But even here we display some characteristics that, though not unique to humans, also distinguish us from other species: most males other than humans do not actually know who their offspring are, nor do the fathers of most species have anything to do with the upbringing of the next generation.

Indulging in intravaginal sexual intercourse without reproductive consequences through the widespread use of deliberate birth control is a practice less than 100 years old (although history records plenty of recipes promoted to accomplish that aim). The true *realization* of ‘sex for fun’ occurred only about 40 years ago with the introduction of the Pill and of IUDs (intrauterine devices) that, for the first time, totally separated the coital act from contraception. Women who use the Pill are temporarily sterile, and thus can indulge in sexual pleasure without the fear of an unintended pregnancy. The decision to reproduce has become a deliberate choice rather than a form of reproductive roulette, which is one explanation why the overwhelming majority of European couples now have fewer than two children per family.

A total separation of sex and fertilization is dependent on two elements. The first is effective contraception: the virtual guarantee of not creating new life during sexual intercourse. The other is its counterpart: the ability to create new life *without* sexual intercourse. Its dawn coincided with the increasing use of artificial insemination, injecting millions of sperm into a woman’s vagina rather than depending on intravaginal penile ejaculation. This low-tech method, using a syringe – or even a turkey baster – underwent a spectacular escalation in technical sophistication in 1978 in England through the birth of Louise Joy Brown, who was conceived under a microscope, where her mother’s egg was fertilized with her father’s sperm. The fertilized egg was reintroduced into the mother’s womb after two days and, following an otherwise conventional pregnancy, a normal girl baby was born nine months later. This technique has since become widely known as *in vitro fertilization* (IVF) – an event that has now been replicated over a million times through the birth of that many IVF babies.

When Steptoe and Edwards² developed IVF in 1977 they did not set out deliberately to make possible the separation of sex from fertilization. They, as well as other clinicians, focused on the treatment of infertility, itself an ethically charged topic. To put it bluntly and brutally: should we treat infertility? From a personal perspective, the drive for successful parenthood is often very powerful. Infertile couples are prepared to undergo enormous sacrifices, financially, psychologically and physically, to produce a live child under conditions where nature has made it impossible. Nevertheless, the question may well be asked whether the realization of parenthood by biologically infertile couples carries some ethical imperative – for or against.

In most of the world – and certainly in Europe and North America – infertility

is, for all practical purposes, considered a disease: a condition that, if possible, should be ameliorated or cured. Rational evolutionary arguments against such an intervention are generally not accepted. The United Kingdom is about to provide the most persuasive affirmative answer through its taxpayers' pocketbooks: within months, IVF treatment for women below the age of 40 will be fully covered under the National Health Service at an annual incremental cost of probably hundreds of millions of pounds. But rather than pursuing the question of the appropriateness of treating infertility, let me focus on some of the implications for the deliberate separation of sex from fertilization – a scenario that in my opinion will increasingly dominate the course of human reproduction in some of the most affluent countries of the world.

Contraception

As already stated, only human beings use contraception. One would think that by focusing predominantly on the hedonistic reasons for practising sex without reproductive consequences, people in such cultures would put the development of improved methods of contraception high on their list of priorities. Yet nothing could be further from the truth. Laypersons, of course, keep dreaming of 'safe, simple, cheap, 100% effective, and reversible' methods of contraception as if a method encompassing all of these desiderata were scientifically or operationally feasible.

In the market-driven economies of the Western world, where essentially all biomedical research is conducted, pharmaceutical companies play an important role in creating new drugs or devices, and an indispensable role in bringing them to the public. Hence, no new contraceptive method will ever reach the consumer without the intervention of the pharmaceutical industry. However, as I predicted in 1970³ and repeated in 1989,⁴ that industry has, for all practical purposes, turned away from any efforts to make *fundamentally new approaches* to birth control (for a list, see Ref. 4) a reality. I emphasize the words 'fundamentally new approaches' to differentiate them from minor modifications of existing methods, which, although representing useful improvements, constitute piddling advances from a scientific standpoint. Of the 20 largest pharmaceutical companies in the world, only two (Johnson & Johnson and Wyeth) do any R&D work in the field of female contraception – most of it consisting of minor improvements in hormonal methods, primarily because of their historical marketing involvement with the Pill and their desire to protect their proprietary market share. The same applies to the only two other companies (Organon in Holland and Schering in Germany) in the next lower tier of drug companies. This lack of interest on the part of large drug companies is strikingly illustrated by the Swiss pharmaceutical colossus Roche, which immediately divested itself of the entire contraceptive line of one of the

pioneers (Syntex) of the Pill, when Roche acquired that company about ten years ago.

The reasons for this lack of interest are manifold³⁻⁵ but the most obvious one is the focus of the pharmaceutical giants on mega-drugs for the ever-increasing geriatric segment of the affluent countries (Japan, Europe and North America). Contraceptives – especially cheap ones – cannot possibly compete with drugs for the treatment of inflammation, cancer, Alzheimer’s or cardiovascular diseases or even with antihistamines! The reasons^{4, 5} for an even greater lack of interest in male contraception are not difficult to understand, foremost being the difficulty of ‘guaranteeing’ return of fertility after 20–30 years of continual use of a ‘Pill for Men’ or the absence of deleterious effects on erectile function and prostate involvement after decades of administering such hormonal agents. It takes little imagination to construct horror scenarios with respect to legal liability – especially in the litigious USA – even though many women will quite justifiably categorize this statement as still another example of the double standard in human reproduction and birth control that men expect them to tolerate.

But with respect to my chosen topic, it does not make any difference if today’s birth control portfolio does not change much in the foreseeable future. It is not the birth control hardware⁵ that has been the causative factor for the impending separation of sex and reproduction, but rather the ‘software’ aspects: the socio-cultural, economic, legal, and political changes during the past 40 years and especially the rapidly changing status of women in those countries where birthrates have plummeted. In fact, if some of the predictions outlined below come to pass, contraception may become superfluous. To illustrate, let me quote a bit of dialogue between two scientists from my play, *An Immaculate Misconception*.⁶

Melanie: Young men and women will open reproductive bank accounts full of frozen sperm and eggs. And when they want a baby, they’ll go to the bank to check out what they need.

Felix: Once they have such a bank account... they might as well get sterilized.

Melanie: Exactly! They’ll just do earlier in life what millions of middle-aged persons are already doing all the time. If my prediction is on target, other forms of birth control will become superfluous.

Felix (Ironic): I see. And the Pill will end up in a museum of 20th century ART?

Melanie: Of course it won’t happen overnight But A... R... T [Assisted Reproductive Technologies] is pushing us that way... and I’m not saying it’s all for the good. It will first happen among the most affluent people... and certainly not all over the world. At the outset, I suspect it will be right here... in the States... and especially in California.

While the frozen egg scenario still requires technical improvements before it becomes a widely practised reality, long-term storage of sperm, coupled with

in-vitro fertilization at the time a couple wishes to conceive, has been proposed⁷ as a practical alternative to male birth control when combined with vasectomy, especially since it does not involve the involvement of the pharmaceutical industry. During the past few decades, millions of men – admittedly, most of them middle-aged fathers rather than young men – have resorted to sterilization (vasectomy) and continue to do so. (Sterilization among both sexes has become so prevalent that, in the US, it is now the most common method of birth control among married couples, even surpassing the Pill). Early sterilization rather than contraception could thus become the norm among the affluent, especially when pre-implantation genetic screening of embryos (*vide infra*) becomes routine. Vasectomy is much simpler and less invasive than tubal ligation in women. Artificial insemination is both simple and cheap. Furthermore, among fertile couples, it has almost the same success rate as ordinary sexual intercourse. But most important for our argument,⁷ fertile human sperm has already been preserved inexpensively for years at liquid nitrogen temperatures. Therefore, provided one first demonstrated along the lines suggested by us⁷ that such storage is possible for several decades rather than just years, those young men convinced of the desirability for assuming more of the contraceptive responsibility, might well consider early vasectomy, coupled with cryopreservation of their fertile sperm and subsequent artificial insemination, as a viable alternative to effective birth control. And since, in most cases, artificial insemination is now equated to in vitro fertilization, it is only logical that I now address the other component of the impending separation of sexual intercourse and fertilization.

In Vitro Fertilization (IVF)

The subject of IVF for the treatment of infertility is not the theme of my presentation and has, in any event, been covered exhaustively in the popular and scientific press for many years. I am addressing the prognosis that fertile couples in the more affluent parts of the ‘Western’ world will resort to the techniques of assisted reproduction for the one or two children they plan to have at a fairly specific time of their life. But why would a fertile couple resort to an expensive laboratory procedure instead of a cost-free pleasurable activity? Two technical advances have made the choice for in vitro rather than conventional fertilization a realistic option (or temptation) for certain couples. The first is a major addendum to the repertoire of in vitro fertilization techniques, specifically intracytoplasmic sperm injection (ICSI), while the second is associated with the dramatic advances in genomics and in genetic testing techniques, especially through PCR (polymerase chain reaction) and DNA chip technology.

ICSI

Impregnation of a woman's egg by a fertile man in normal intercourse requires tens of millions of sperm – as many as 100 million in one ejaculate. Successful fertilization with one single sperm is a total impossibility, considering that a man ejaculating even 1–3 million sperm is functionally infertile. But in 1992, André C. Van Steirteghem and collaborators from the University of Brussels published a sensational paper⁸ in which they announced the successful fertilization of a human egg with a *single* sperm by direct injection under the microscope, followed by reinsertion of the egg into the woman's uterus. ICSI – the accepted acronym for 'intracytoplasmic sperm injection' – has now become the most powerful tool for the treatment of male infertility: over 100,000 ICSI babies have already been born since 1992.

The operational and ethical implications of this discovery are enormous and extend way beyond the simple treatment of male infertility due to oligospermia (insufficient number of sperm). For some time now, I have felt that this topic should be discussed beyond the confines of an academic lecture or technical article and I have thus tried to bring it to the attention of a much wider public through non-conventional means. I have chosen three: a science-in-fiction novel (*Menachem's Seed*⁹); a play (*An Immaculate Misconception*⁶); and most recently, a 'pedagogic wordplay' (*ICSI – Sex in the age of mechanical reproduction*¹⁰) designed to fit within the time and practical constraints of a 40-minute lecture. I shall use a few excerpts from this wordplay* to show how some of the ethical issues of ICSI are raised in purely dialogic form. The setting is a putative TV interview between a female moderator (Isabel Youngblood) and a male reproductive scientist (Felix Frankenthaler).

The issue they are discussing is the ethics of two problems that are often associated with IVF (rather than just specifically ICSI): the frequency of multiple births and the fate of stored, unneeded embryos.

Frankenthaler: There is one point that both the audience and my host here should be aware of. As in all instances of assisted reproduction by in-vitro fertilization techniques, there was a high incidence of multiple pregnancies: 128 twins and 34 triplets out of 382 successful ICSI conceptions.

Youngblood: You're having multiple pregnancies because you transfer more than one embryo – I believe at least three – into the woman's uterus to increase the odds. No wonder you get so many twins and triplets.

Frankenthaler: Fair enough. Bear in mind, however, that many of our patients are older couples. And that women over 40 suffer pregnancy loss six times more

* Instead of the standard dictionary definition of 'wordplay', I refer to a scripted dialogue with adversarial tone that is read out loud (rather than learned by heart) in a class or other academic venue by more than one person in lieu of a conventional, monologist lecture. The German word '*Wortgefecht*' seems particularly apt.

often than women below 35. That's why it is important to increase, as you say, the odds. Still, every once in a while, all of them implant – we hit the jackpot, so to speak. So we counsel the couple – especially in the case of triplets, with all the associated risks to the mother and the potential babies – to consider selective reduction–

Youngblood: Why not call a spade a spade?

Frankenthaler [Quick and defensive]: Because we're not playing cards, nor do we wish to gamble.

Youngblood: Still – why not say abortion?

Frankenthaler: We are in the business of *creating* life, not *terminating* it. Selective reduction means *increasing* the chances for completing a pregnancy. [FRANKENTHALER is clearly bothered by introduction of abortion issue.] With all of our accumulated experience, we now encounter such a high success rate that we find ourselves increasingly with supernumerary embryos, which we cryopreserve.

Youngblood: Supernumerary?

Frankenthaler [Jaded]: I assume you're not requesting a dictionary definition?

Youngblood: Just questioning your use of terms. Isn't 'supernumerary' just another way of saying 'rubbish'? Aren't you coming awfully close to playing God? Deciding who gets to live?

Frankenthaler: Since you seem to be so concerned about accurate terminology, let me point out that '*supernumerary*' is not judgmental. It's just a fancy word for 'excess'. You must allow me at least some big words. Otherwise, how can I impress you? That's why we *cryopreserved* the excess embryos – 'froze them', in ordinary English – rather than discarding them. Satisfied?

Youngblood: You're just begging the question, aren't you? What is the ultimate fate of these [uses purposely a precious, possibly sarcastic manner of enunciation] *cryopreserved, supernumerary* embryos?

Frankenthaler [In perceptibly lower tone]: It's not really a medical decision, is it? First, to whom do the embryos belong? Once the mother has given birth to the desired number of babies by ICSI, she may not wish to have more implanted into her. Should other women then use them? Could they be sold by the egg donor and purchased by an infertile woman – even a postmenopausal one – for transfer into her uterus so that she becomes a quasi-biological but not genetic mother? [Becomes progressively more agitated.] And if not, what then? Do we simply keep them indefinitely? Use them in research? Or are they junk and turn to garbage when they are discarded? Who decides what to do with that ever-increasing number of cryopreserved embryos?

Youngblood: Precisely. So who does?

Frankenthaler: I am the one who posed the question. It's for you [turns to the unseen camera]... all of you, to answer.

There are several highly contentious issues that have arisen primarily because of the uses to which ICSI can be put. Take for instance selection of the baby's sex.

Youngblood: There's one more thing. If ICSI injection of a single sperm followed by fusion with the egg is successful, the road to new life is open. But what form of life? Male or female? Why don't you tell us a bit about how that's decided.

Frankenthaler: Now that's easy. The sex of the offspring will always be controlled by the sperm – *never* by the egg. If the sperm contains a sex-determining chromosome called X, the child will be a girl; if it contains a sex-chromosome called Y, a son is born.

Youngblood: So men who have complained for millennia that their wives didn't provide them with sons have no one to blame but themselves. Trading wives won't do it. It will always be the roll of the seminal dice.

Frankenthaler: Well put! 'Seminal dice'. [Chuckles.] And never loaded. If Henry VIII had viewed tonight's show, some of his wives might have survived.

Youngblood: I read somewhere that it's now possible to separate X- and Y-containing sperm. I don't know by what method–

Frankenthaler: Flow cytometry.

Youngblood: Whatever. My question is: if that separation is now possible, could one select a Y-sperm, and use it with ICSI to guarantee a son? In other words, *load* the seminal dice?

Frankenthaler: It's trivial. With ICSI, the answer is a definite yes.

Youngblood [Suddenly agitated]: You call guaranteed sex predetermination *trivial*? And what then? Preponderance of male children? Overwhelming preponderance? Will that lead to legalized prostitution or polyandry or more wars or–

Frankenthaler: Stop! Is it fair to lay all that at *my* feet? *Any* scientist's feet? When I used the word 'trivial', I meant the technical aspects. I meant, yes, it's easily possible with ICSI to load the dice. I intended no judgement of the social consequences – none at all. I certainly do not recommend establishing reproductive casinos full of ICSI-loaded seminal dice. Such uses – and hence, such questions – do not concern me.

Youngblood [Stiffly]: Shouldn't you *scientists* worry about the ethical problems raised by ICSI? *Before* the genie escapes from the bottle?

Frankenthaler [Sardonic]: '*Before* it escapes?' It's out, and there is no way of putting it back in. All of us, including you, will have to learn to live with ICSI.

Youngblood: So you agree there is a problem with ICSI when using purposely-separated X- or Y-chromosome containing sperm?

Frankenthaler [Reluctant]: Social problems? Yes. But scientific... I mean technical ones? [Shakes head.] No, I don't see any there.

Or what about the problems raised when ICSI is used with men, who are genetically infertile, because they contain no mature sperm whatsoever?

Youngblood: Initially, you and your colleagues set out to promote ICSI as a treatment for male infertility caused by an insufficient number of sperm. But lately, have you not branched out to treating infertility from other causes, in some of which the sperm isn't even mature? [Again looks at her notes.] In fact, extreme cases such as men, who lack a vas deferens?

Frankenthaler: Quite correct.

Youngblood: But since the vas deferens is the duct in which the sperm is stored and transported, men born without one have not the faintest chance of becoming fathers. Yet you and your colleagues feel that such severely impaired men – I mean *reproductively* impaired men – are also entitled to ask whether such new reproductive technologies can make them fertile. Is that a fair representation of the facts?

Frankenthaler: It is.

Youngblood [Seemingly innocently]: Would you care telling our audience about the results?

Frankenthaler: As you stated, we felt that such men need not necessarily be excluded from biological fatherhood, so we tried the ICSI procedure with a few volunteer couples. Once these defective sperm were injected by the ICSI procedure into the egg, everything went according to plan!

Youngblood: Aren't you now operating on the very edge of permissibility? Or even beyond it?

Frankenthaler [Frowns, but attempts levity]: Some people will tell you that the only way to find an edge is to fall over it.

Youngblood: Dr Frankenthaler, you just mentioned your ability to offer genetic fatherhood to men who are born without a vas deferens. Right?

Frankenthaler: Right.

Youngblood [Reads from her notes]: Isn't it a fact that such absence of the vas deferens is considered an indicator of cystic fibrosis? [Her voice acquires an edge of sharpness.] And that such men, who, of course, are ordinarily infertile, could now have children via ICSI and thus run a significant risk of passing cystic fibrosis on to the offspring? Inheriting the uninheritable? Doesn't that worry you, Dr. Frankenthaler? It worries me. It worries me a great deal.

Frankenthaler [Let's out audible sigh]: Of course, you're right about the cystic fibrosis risk and the couple is so advised. We took such an eventuality into consideration at the very outset. We insist on genetic screening of both partners and on pre-implantation as well as later genetic screening of the embryo. If we

find an extra chromosome, indicating mutation, we urge termination of the pregnancy. For your information, so far we have not found any higher incidence of mutations than in ordinary pregnancies. Now, under these conditions, would you not offer ICSI to a man with congenital bilateral absence of the vas deferens?

Youngblood [Wags head]: You're still challenging some biological dogmas that were considered inviolable. More than any previous technique, ICSI bypasses several steps that presumably serve as nature's screening mechanisms for deficient sperm. You skip the acrosome reaction. You eliminate independent penetration of the zona pellucida and of the egg-membrane. And now you tell us that you can even bypass sperm maturation in the epididymis. Given that one human generation is equal to about 20 years, it will take at least that long before the genetic effects of ICSI can be fully evaluated. [Again wags head.] By the way, quite separate from the issue of cystic fibrosis, what if the father's infertility is passed on to the son? Are you willing to perpetuate that problem?

Frankenthaler: If that's the only thing worrying you, you can relax. All we're perpetuating is a different form of fertilization. If the son is sterile, you'll simply use ICSI again. Like father... like son. What's wrong with that? Why are people so preoccupied with non-coital methods of reproduction? In the final analysis, we are only arguing about differences in delivery vehicles: penis versus pipette.

I shall now leave the TV studio of my pedagogic wordplay with its dialogic presentation mode to resume the conventional monologist format of an academic article or lecture.

Pre-implantation embryonic genetic screening

While there are many other contentious issues associated with ICSI that could be debated – for instance, the successful use of sperm aspirated from a recently deceased man (24–30 hours post mortem) to produce seemingly healthy babies – it is now time to address one of the most controversial aspects of the impending use of assisted reproductive technologies by fertile couples. In the preceding example, I cite a use of genetic screening that is hardly ever condemned, namely searching for genetic markers associated unambiguously with serious genetic diseases such as cystic fibrosis, Tay-Sachs disease, Huntington's disease, Down's syndrome (mongolism) and the like. But what about the abuse of such technology when the a priori existence of such diseases is not the issue?

Parenthood in humans is driven largely by a deep, personal association with one's children, indeed by obsessive identification with them. It takes little imagination to relate the desire for such parenthood, especially when limited to only one or two children, to the practice for some form of micro-eugenics within the nuclear family. Many of these families do so already at the Lamarckian level by exposing their precious offspring to the best possible environment: the best

school, the private lessons, the newest computer Why should they not be tempted to extend this to the Mendelian level?

For instance, haemophilia is carried forward through the mothers, meaning that while male haemophiliacs do not transmit the disease to their children, daughters born from such fathers become carriers of the disease to their own sons. Why automatically condemn the Spanish family with a history of haemophilia that decided to use only male embryos during in vitro fertilization to avoid the danger of haemophilia in their eventual grandchildren, thus jumping a generation to stamp out the disease in that family?

In the above cited example, the selection was made purely on the basis of sex. But consider the British family¹¹ with an infant suffering from Diamond Blackfan anaemia, whose life expectancy could only be improved by administration of primitive stem cells from an immunologically identical sibling, thus necessitating more extensive pre-implantation embryonic screening. Although naturally fertile, the couple chose in vitro fertilization in order to select an embryo with the necessary criteria for implantation into the mother's uterus. Yet the Human Fertilisation and Embryology Authority, whose permission was needed to perform the procedure in the UK, denied it in 2003, whereupon the parents indulged in the obvious subterfuge – medical tourism – by going to the USA for the necessary IVF treatment. The legal and perhaps even moral argument against granting permission was based on the belief that such genetic screening was not done for the benefit of the new child (i.e. screening for some potential fatal disease marker) but rather for that of the sick child, thus making the second sibling a 'designer baby'.

Yet theirs was not the first such case! Three years earlier at the Fairview-University of Minnesota Medical Center, a Colorado couple chose precisely the same route. Their daughter suffered from Fanconi anaemia, a genetic condition preventing the production of bone marrow and thus a certain prescription for early death. With their second child, by pre-implantation screening of the embryos for the Fanconi anaemia marker, they were able to guarantee that their next offspring (a son named Adam) would be free of that disease and could serve as a compatible tissue donor for his 6-year older sibling. In fact, transplant of umbilical cord stem cells from the 'made-to-order' Adam caused the older child to start making platelets and white blood cells on its own.

I have already alluded to, and will once more refer to, pre-implantation embryonic genetic screening, a procedure primarily available to the affluent in the affluent countries. But given the rapid progress in human genomics and the many technically feasible methods of rapid genetic screening, what will keep prospective IVF parents from screening their own embryos so as to transfer only the 'best' back into the mother? Who will define 'best'? Few people will argue that prospective parents may wish to discard embryos that show the markers for

Down's or Huntington's Syndrome, or markers for genetically transmitted cancers – prospective parents, who follow the motto 'better be tested now than diagnosed later'. But where will the line be drawn? As we move toward the slippery slope of tailor-made progeny, the gulf between the haves and have-nots is widening enormously.

Peri- and post-menopausal pregnancies

Although many may consider some of the scenarios here as 'unnatural' or worse, every one of them has now been realized or is about to be implemented. So let me end with the question of the ethics of peri- or post-menopausal pregnancies, which has become particularly acute since the invention of ICSI.

Until very recently, the onset of menopause was welcomed by many women as the release from continuous pregnancies caused by unprotected and frequently unwanted intercourse. But the arrival of the Pill and other effective contraceptives, coupled with the greatly increased number of women entering demanding professions that cause them to delay childbirth until their late 30s or early 40s, now raises the concern that menopause may prevent them from becoming mothers altogether. Whereas reproductive technology's focus during the latter half of the 20th century was contraception, the technological challenge of the new millennium may well be conception (or infection, if one focuses on sexually transmitted diseases).

In progressively more geriatric societies such as Western Europe, where 20% of the population is already, or will soon be, over the age of 60, and older people are increasingly healthier than they used to be, a woman who becomes a mother at 45 could raise a child for a considerably longer time than could a 20-year-old at the beginning of the last century. Of course, motherhood at an older age is physically, psychologically, and economically suitable only for certain women, but at least the choice is now available in wealthy countries. It must be emphasized that this increased emphasis on artificial fertilization techniques and even surrogate parenthood is a characteristic of the affluent, 'geriatric' countries and often of women who did not wish to make the choice between motherhood and profession at an early age. Even within these countries, the cost of such reproductive technologies (frequently not covered by insurance) is such that only the more affluent citizens can afford them. Three-quarters of the world's population is represented by the 'paediatric' countries of Africa, Asia and much of Latin America, where over 40% of the population may be below the age of 15 and where the control of fertility rather than the treatment of infertility will remain an important social aim for some time to come.

Still, let me end with a pertinent dialogue between the 38-year old reproductive biologist, Melanie, and her medical colleague, Felix, from my play, *An*

Immaculate Misconception,⁶ which summarizes one of the best reasons why fertile couples will increasingly start to resort to IVF techniques for the one or two babies they plan to have.

Melanie: In your IVF practice, it's not uncommon to freeze embryos for months and years before implanting them into a woman.

Felix: So?

Melanie: So take frozen eggs.

Felix [Dismissive]: I know all about frozen eggs... they're very different from embryos. There're even problems with just freezing them. And after thawing, artificial insemination hardly ever works Do you want to hear the reasons for those failures?

Melanie: Who cares? What I'm doing isn't *ordinary* artificial insemination... I'm not exposing the egg to lots of sperm and then letting them struggle on their own through the egg's natural barrier. With ICSI, I inject right *into* the egg! Think of those women... right now, mostly professional ones... who postpone childbearing to their late thirties or even early forties. By then, the quality of *their* eggs... their relatively few remaining *own* eggs... is not what it was when they were ten years younger. [Becomes progressively more emphatic]. So once the cryopreservation of eggs is perfected... and that's just a matter of time... with ICSI, such women could draw on a bank account of their frozen *young* eggs and have a much better chance of having a normal pregnancy later on in life. I'm not talking about *surrogate* eggs—

Felix: Later in life? Near... or even past the menopause?

Melanie: You convert men in their fifties into successful donors—

Felix: Then why not women? Are you serious?

Melanie: I'm not sure that we reproductive scientists ought to open the door to postmenopausal pregnancies. But reducing the hazards of the biological clock by several years – say to the middle or late forties? I see no reason why more women shouldn't have that option.

Felix: Well – if that works... you won't just become famous... you'll be notorious.

Melanie: I'll risk the notoriety. The fame, I'll share with you.

Felix [Mollified]: Okay So you've got a new method of fertilization.

Melanie: Think beyond that... to a wider vision of ICSI. I'm sure the day will come – maybe in another thirty years or even earlier – when sex and fertilization will be separate. Sex will be for love or lust—

Felix: And reproduction under the microscope? Sure... infertile people are willing to do that all the time. [Pause.] But fertile couples?

Melanie: And why not?

Felix: Reducing men to providers of a single sperm?

Melanie [Laughs]: What's wrong with emphasizing quality over quantity? I'm not talking of test tube babies or genetic manipulation. And I'm certainly not promoting ovarian promiscuity, trying a *different* man's sperm with each egg.

Felix [Chuckles]: 'Ovarian promiscuity!' That's a new one.

Melanie [Now serious and deliberate]: Each embryo will be screened genetically *before* the best one is transferred back into the woman's uterus. It's that ability for pre-implantation genetic screening of the embryos that will convince fertile couples... knowing they'll improve the odds over Nature's roll of the dice.

Conclusions

So where does this impending separation of sex and fertilization leave us? On 15 October 1951, we completed the first synthesis of an oral contraceptive steroid in our laboratory and thus set in motion the effective separation of coitus and contraception. Half a century later, we face the impending separation of coitus and conception. Does that mean that these two steps have made love superfluous?

As I already stated in my reflections⁵ at the 50th anniversary of the Pill's birthday, in the next century, love or lust for one's partner will continue to be the principal incentive for sexual congress. The decision to produce a child involves a different kind of love, ideally tempered by responsibility and serious reflection. The recent advances in contraceptive and reproductive technologies now permit us to make that decision rationally as well as lovingly, but whether we shall display the necessary wisdom and restraint remains to be proven.

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About the Author

Carl Djerassi, novelist, playwright and professor of chemistry emeritus at Stanford University, was born in Vienna and is one of the few American scientists to have been awarded both the National Medal of Science (for the first synthesis of an oral contraceptive) and the National Medal of Technology (for promoting new approaches to insect control). Djerassi has published over 1200 articles dealing with the chemistry of natural products (steroids, alkaloids, antibiotics, lipids and terpenoids), and with applications of physical measurements (notably optical rotatory dispersion, magnetic circular dichroism, and mass spectrometry) and computer artificial intelligence techniques to organic chemical problems. In medicinal chemistry he was associated with the initial developments in the fields of oral contraceptives (Norethindrone), antihistamines (Pyribenzamine) and topical corticosteroids (Synalar). He has also published five novels, two autobiographies and six plays. He resides in San Francisco and London.

