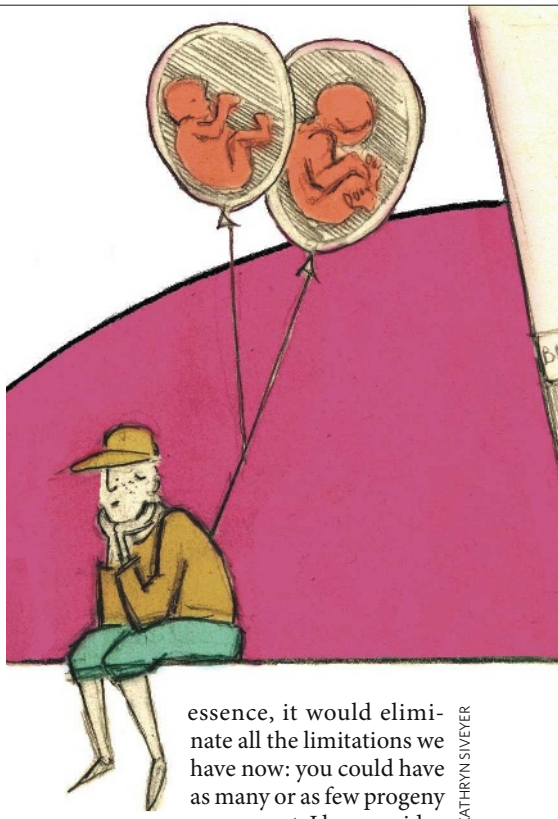
SPECIAL REPORT

Making babies: the next 30 years

Louise Brown, the first test-tube baby, was born 30 years ago this month after being conceived outside the body using *in vitro* fertilization (IVF). **Helen Pearson** asks what developments in reproductive medicine could have an equivalent impact in the next three decades.



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Davor Solter, developmental biologist at the Institute of Medical Biology (IMB) in Singapore

The goals will remain the same in that we'll be trying to give children to those who can't have them and remove children from those who don't want them. I think IVF has gone about as far as it can.

Next I expect that germ cells — sperm and eggs — will be successfully derived from induced pluripotent stem (iPS) cells [cells that have the potential to develop into any of the body's cell types]. It will be possible to make iPS cells from skin cells, to make germ cells from these, and then combine them to make human embryos.

It means every person regardless of age will be able to have children: newborn children could have children and 100-year olds could have children. It could easily happen in the next 30 years.

I have no idea if the technique will be used, but it means you could have millions of gametes that could be combined at will. Today you can't experiment on human embryos because it's considered morally repugnant — and they are difficult to get. If embryos could be grown in culture like any other cell line, this latter problem would disappear. It would mean you could introduce any kind of genetic modification. The cell lines could be used to correct a mutation or to engineer an improvement, and used to make a mutant embryo for research purposes. They'd become like any other type of cell line. They would become objects and would be used as objects.

I have no idea what kind of moral value or rights we would give to those embryos. We'll probably go through the same agonizing we did with IVF. It could be terrible to begin with, but then it'll become a fact of life. Maybe 20–30 years from now we'll read in newspapers that someone made 20,000 embryos and studied their development, and we'll decide it's OK.

Another thing I predict for this brave new world is the use of artificial placentas. In essence, it would eliminate all the limitations we have now: you could have as many or as few progeny as you want. I have no idea how easy it would be. I can visualize a fetus floating freely in fluid and the umbilical cord attached to a machine. But I don't know how much implantation is necessary. The fetus floats freely, but for the blastocyst [early-stage embryo], the placenta might be necessary for normal morphogenesis [organ development, for example].

Looking back

Howard Jones, professor emeritus at Eastern Virginia Medical School in Norfolk who in 1981 produced the United States' first IVF baby

At that time, we doctors could help only around half of the couples that came to us with fertility problems. We mainly used surgical or endocrinological methods.

I first met Bob Edwards in 1964 when he came to Johns Hopkins, where I was an assistant professor, and he asked for some human eggs because in the United Kingdom they were having trouble getting them.

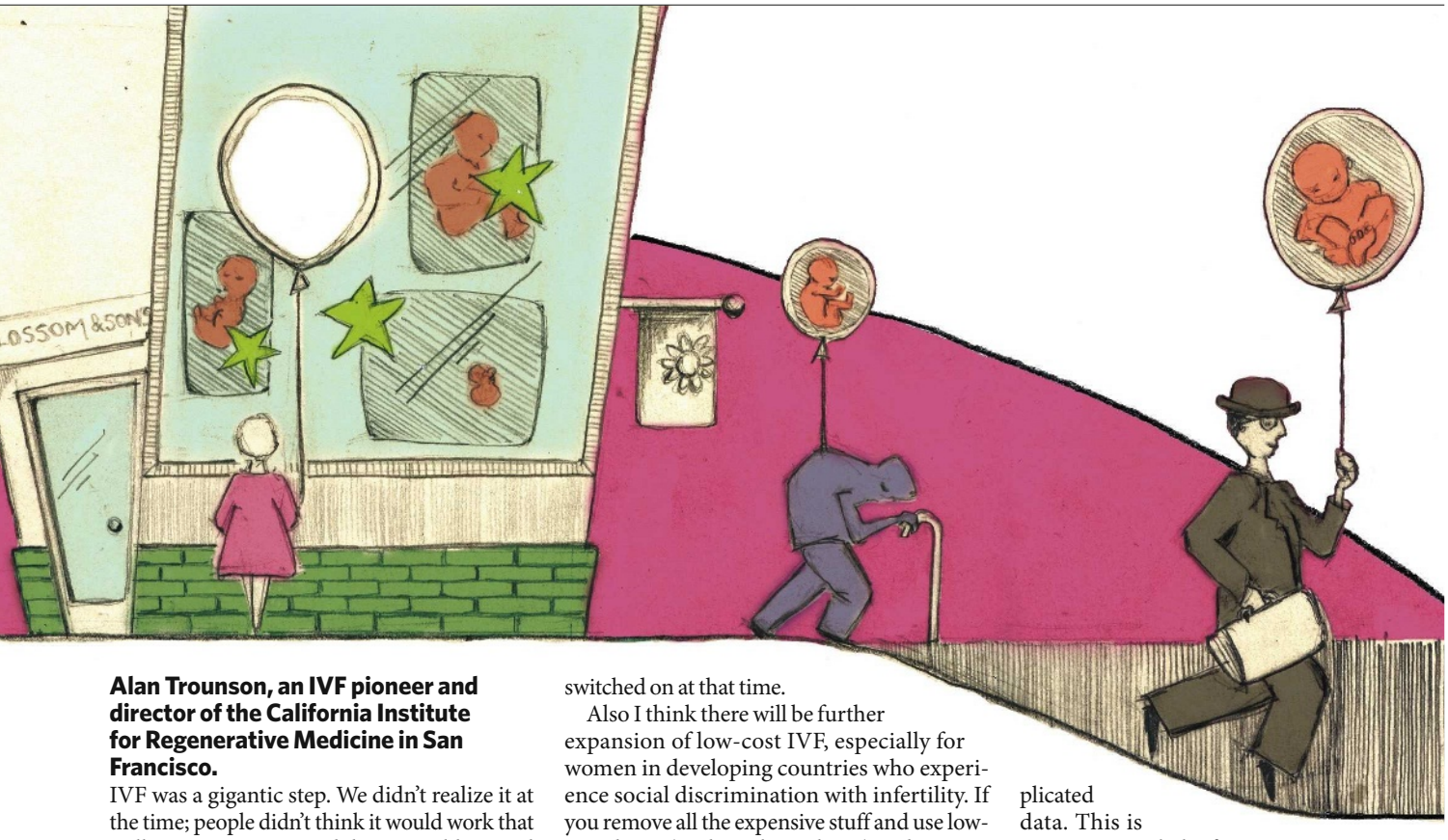
Five years earlier, Min-Chueh Chang had shown that IVF was possible in rabbits. But human sperm had to be 'capacitated' before it could be used to fertilize the egg, and this seemed to occur in the female genital tract. Bob's idea was to capacitate the sperm. My job was to give Bob parts of the female genital tract such as cervical mucus and bits of uterus lining to see what worked. In retrospect I think *in vitro* fertilization did actually occur at Hopkins in 1965.

Bob went back to England and kept trying. Capacitation was not the problem as it turned out. The key was to get a culture medium agreeable — it had to do with the acidity and oxygen levels. It turns out the human requires a slightly different culture medium from animals.

It took Bob some 15 years of trying until Louise Brown was born. We said we'd try for three years and then reconsider. We had 41 attempts with no pregnancies at all. Then, in 1981, my wife suggested we use pergonal to stimulate egg production. We did it and the 13th attempt was successful. These drugs are now standard throughout the world and my wife deserves the credit for that. It worked in about 18 months: the baby was called Elizabeth Carr, she was born in December 1981 and I keep in touch with her. There had been about a dozen IVF babies by then.

In the United States there was a hearing to get a 'certificate of need', which is required for all new procedures. It went on from 2 till 8 p.m. and the 'right-to-lifers' brought in people to testify, and we brought in scientists to testify. The main argument they had was that as several embryos were implanted and only one developed, IVF was causing the others to abort. There was lots of publicity and subsidiary hearings before we got our certificate of need.

It interests me that society has always wanted to regulate IVF processes — IVF is unique in that regard to all other procedures, such as heart or lung surgery — why is that? What are they trying to regulate? It probably has something to do with the mysteries of reproduction. I think we should move on and treat it like any other procedure. **H.P.**



Alan Trounson, an IVF pioneer and director of the California Institute for Regenerative Medicine in San Francisco.

IVF was a gigantic step. We didn't realize it at the time; people didn't think it would work that well. We never envisaged that it would expand so dramatically around the world.

Ethics keeps moving. What was once seen as dangerous goes on to be seen as within the confines of acceptable risk. Probably the major development in the field will come from something we've never thought about.

I think it will be possible that we'll be able to extend the fertile period for women by producing germ cells from iPS technology, or by a variant of nuclear transfer, so somatic cells [which make up most of the body's cells] become germ cells and are refreshed genetically. I think this will happen, and it raises a lot of ethical issues about safety and the children. There will be concerns raised over whether the fertile period should be extended beyond its natural point. I think people should be given the choice.

The idea needs first to be established in animal models. We need to look at lifespan because we don't know the impact of reprogramming cells in this way. Another issue is whether we should bank cells from people when they are very young to avoid the accumulation of genetic errors that occur as we get older.

We might see a move towards artificial chromosomes and 'genetic cassettes' that can be inserted at the embryonic stage to correct particular diseases, such as Huntington's. These might be inducible cassettes that can correct for an abnormality that occurs late in life and switched on at that time.

Also I think there will be further expansion of low-cost IVF, especially for women in developing countries who experience social discrimination with infertility. If you remove all the expensive stuff and use low-cost drugs (such as clomiphene) and remove just one or two eggs, and only transfer one embryo, it can be done for less than US$100.

Susannah Baruch, director of reproductive genetics at the Genetics and Public Policy Center at Johns Hopkins University in Washington DC

Right now preimplantation genetic diagnosis (PGD) is used during IVF to look for single gene disorders in, for example, a family in which a child has already died. I think genetics will continue to play a big part in assisted reproductive technology. The bigger question is: what will people be testing for?

There's speculation that people will have designer babies, but I don't think the data are there to support that. The spectre of people wanting the perfect child is based on a false premise. No single gene predicts blondness or thinness or height or whatever the 'perfect baby' looks like. You might find genetic contributors but there are so many environmental factors too.

More likely is that you'll have a set of embryos and you'll know every single thing about every gene in every embryo. For example, one embryo will have three genes associated with tallness, two for weakness, three for poor vision and some for disease; and the second embryo will have some other set. They're very complicated data. This is not creating a baby from scratch. None of us is a perfect specimen and none of our embryos will be either.

I think you'll end up with a lot of information available to parents and it's less obvious how useful that information will be and how many parents will want it. I think the technology will be there within ten years to be able to know without harming the embryo, but I don't know whether it will become widely used. There are bound to be some parents who want it, and then the dilemma is deciding what you tell your children about the choices you made.

Will people choose IVF to get that genetic option? IVF is expensive and uncomfortable. The old-fashioned way is cheaper and more fun and that won't change in 30 years.

Alastair Sutcliffe, a paediatrician who studies the health of children after IVF at University College London

Litigation is a big driver in medicine. With the increasing availability of IVF, there will be more emphasis on safety. Not enough is known about the long-term health of the Louise Browns of this world — if there is a problem, it will be unexpected.

The concern is over whether the culture media used to nourish the cells and embryo before implantation has epigenetic effects [changes to the way a person's genes are expressed]. For

example, there is some evidence that Beckwith Wiedemann syndrome is more common in children conceived through IVF, but whether this is a true effect is unclear. I always say it's rare — but if your child's got it …

And the fertility of those IVF children as they grow up is of interest. What are the subtle effects? I want to look at epigenetic markers in these people. I'm one of the few people who can do this because of the cohort of children that I have. I think it's a quantum leap to say that because a couple was infertile the child will be too.

Scott Gelfand, director of the Ethics Center at Oklahoma State University in Stillwater

There is some research aiming to increase embryo survival and the likelihood that IVF will work. There are also people who are working on the other end — at the moment babies can only survive from around 22 weeks, but in future fetuses this could be extended to those that are 12 weeks. Someone could join these two advances together and we could have complete ectogenesis [in which the fetus develops outside the body in an artificial uterus]. I find it interesting and scary.

Those who work on artificial-womb technology aren't talking openly about it anymore. My guess is it's a potential lightning rod in our culture. There are some very interesting moral and ethical implications associated with artificial wombs. Certain conservatives might think it shouldn't be used but some might think that it could meet the test of Roe *vs* Wade — that it protects the privacy of the woman while preserving the rights of the fetus. If an artificial womb were developed, the government could pass a law that requires people who have a termination of pregnancy to put the fetus into one of these wombs. That's the fear of many pro-choice theorists. There are around 1 million abortions per year in the United States and there would have to be labs throughout the country, but if we put all these in artificial wombs and then put them up for adoption we would have one million more babies. It would be a nightmare. When I talk to some anti-abortionists about that, they really shudder.

Even in terms of insurance: if it became economically competitive with other forms of gestation, insurers might compel a person to use it to avoid premature birth or fetal alcohol syndrome. It's something that really needs to be talked about. Will it happen? Dolly was a complete surprise to everybody …

Miodrag Stojkovic, stem-cell biologist at the Prince Philip Centre of Investigation in Valencia, Spain

Will we see a cloned baby? It could happen any day because of a lack of regulation [in some countries]. To my knowledge people are already trying to do reproductive cloning. Technically it is possible — a paper this year showed that you could derive human blastocysts after nuclear transfer [in which the nucleus of one cell is transferred to another cell] and our previous work has shown it is possible to grow human embryos to the blastocyst stage too. The only problem is the logistics of getting hold of enough viable human oocytes [eggs]. If we can make human oocytes from stem cells, it might be easier.

The field is developing so fast that some people can't follow what happens and are scared. There are plenty of movies in which scientists clone humans and use their organs for tissue donation, but this is not the reality. There is no medical need to clone a human. If we can make artificial gametes there would be no need to do it. The future is not about reproductive cloning, that's a very, very detrimental technique.

Humans are getting more and more lazy when it comes to reproduction. Male fertility is declining and parents are deciding to have their first child at 40.

We need to learn what the embryo needs to result in a pregnancy — you can have excellent embryos in IVF and no pregnancy. But this can only be answered with human embryos. There is plenty we don't understand about embryo–mother communication. I don't think 30 years will be enough to answer those questions.

Zev Rosenwaks, director of the Center for Reproductive Medicine and Infertility in New York

I see the technology going towards possible eradication of infertility altogether. With nuclear-transfer technology or cell modification, I think we'll be able to generate sperm and eggs for anybody.

I think we've potentially reached the limit of biology in terms of the female's eggs, so artificial gametes might overcome that. In the best cases, success rates for IVF can exceed 70% with one cycle. The limitation is that we can't ensure the embryo is normal. I think there will be methods to evaluate the embryo for its viability and genetic competence in a non-invasive way, without having to remove cells. Cell-culture media is one way, as are micro-imaging techniques that look at chromosomal make-up. It could increase the success rate of IVF if we were better able to select the best embryo with markers such as metabolomics or with imaging techniques we can't even imagine today.

We can already take a cell from an embryo to create a cell line. In the future, this may become routine.

Régine Sitruk-Ware, reproductive endocrinologist and executive director of research and development at the Population Council in New York

If we look at centres in reproductive sciences funded by the National Institutes of Health, there are more than twenty on IVF and only a handful on contraceptive research. It's more politically correct to help people get babies than the reverse, but it's important to have a balance.

Many current contraceptive methods have side effects or they're not effective. We can do better. We're hoping it might be possible for men and women to alternate taking contraceptives and that we can develop non-hormonal methods with fewer side effects that are very specific in targeting an enzyme or protein in the reproductive process, such as one that stops the ovum from maturing, or sperm from entering the egg. ■

See Editorial, page 253, and Essay, page 280.