Dr. Hugo Verhoeven: “I’m Hugo Verhoeven and I’m a member of the Editorial Board of OBGYN.net. I’m reporting from the 9th Annual Congress of the International Society for Gynecologic Endoscopy at the Gold Coast in Queensland, Australia. It’s my exceptional honor to interview Dr. John Yovich from the Pivet Medical Center in Perth, Australia. John is one of the absolute pioneers in the field of in-vitro-fertilization. John, good afternoon and thank you for having time for this interview.”

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Dr. John Yovich: “It’s my pleasure Hugo, nice to catch up with you, one of the pioneers in the field of male and female infertility microsurgery.”

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Dr. Hugo Verhoeven: “Many, many years ago you were one of the first people who were active and successful in in-vitro-fertilization. When you started with in-vitro-fertilization, did you realize what was going to happen, did you expect that you were working on a technique that would change the world? What were your expectations at the time you started IVF?”

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Dr. John Yovich: “Hugo, I started IVF in 1976. I traveled from my home in Western Australia to London in that year with the knowledge that current infertility treatments were not very effective. It was still the early era of using ovarian stimulation treatments, mainly clomiphene and just a little bit of exploring gonadotrophins beyond WHO Type I amenorrhoea/anovulation cases. In fact, the main hype of that time centered around the use of bromocriptine and even trans-sphenoidal pituitary surgery for hyperprolactinaemia was common for a short period.

As far as tubal reconstructive surgery was concerned, many of us newer consultants realized that traditional surgical procedures provided minimal benefit for fertility. In fact, extensive pelvic adhesions were common sequelae and even Sir Norman Jeffcoate, earlier British doyen and teacher of gynecology, said at his retirement in the late sixties that even in his own hands, pelvic surgery generally contributed very little to infertility. Those women who did conceive following his surgery, probably did so on the basis of chance alone! However it is proper to add that whilst IVF was being developed, colleagues such as Gomel, Winston and yourself were developing the concept of microsurgery concurrently and this did result in appropriate benefits, which is now further proceeding down the line of laparoscopic pelvic surgery.

Another driving force for my interest in IVF was that we were beginning to realize in the early seventies that a major social revolution was underway with women deferring their first pregnancy to later than the traditional 18 to 23 years, which was the norm of the pre-Pill era i.e. before the sixties.

So, to answer your question Hugo, when I began to establish a human IVF research project with Professor Ian Craft in London in 1976, my expectation was that this would be the method to provide a total answer to the mysteries of conception and pregnancy, even though there had been no success with the technique, and even then the scientific and medical worlds were strongly expressing negative views about the work at that time.”

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Dr. Hugo Verhoeven: “Tell us about the early hurdles you faced in establishing a successful program, John.”
Dr. John Yovich:

“The world knows that the earliest pioneers, Patrick Steptoe and Robert Edwards achieved the first viable IVF success with the birth of Louise Brown in July 1978. This vindicated their persistent research in the face of daunting international criticism, which also included the argument that they were somehow usurping the role of God! However, the techniques used in that first successful case were problematic for those of us wanting to establish a useful therapeutic program to treat large numbers of subfertile couples.

As you know treatment programs today involve controlled ovarian stimulation of the female partner so that doctors can offer 25-35% chance of pregnancy in the collection cycle, and usually a number of cryopreserved embryos for further chances if and as required. Certainly, Steptoe and Edwards had these ideas in mind at the beginning of their work but they recognized several problems, including adverse hyperstimulation effects and luteal phase disorders which were directly related to the degree of urinary estrogen output. Nonetheless, after a decade of work utilizing ovarian stimulation they did achieve an early pregnancy in 1976, which unfortunately proved to be an ectopic in a defective fallopian tube. They utilized progestagen support in that case and kept the pregnancy going until the 11th week when Patrick had to perform a laparotomy for salpingectomy. Not only was the patient in grief about her loss, but Edwards and Steptoe had suffered great anguish during that pregnancy, feeling very frustrated at its outcome. Steptoe promoted the view at that time that irreparably damaged fallopian tubes should be completely removed prior to IVF, and Edwards resolved to develop a technique of tracking the natural cycle to collect the single oocyte from unstimulated ovaries. In fact, Louise Brown and a subsequent male infant resulted from a series of such unstimulated IVF cycles. They utilized a bioassay kit known as HiGonavis to detect the LH surge in urine samples tested several times daily.”

Dr. Hugo Verhoeven:

“So the only way for detecting the moment of ovulation was a biological test?”

Dr. John Yovich:

“At that stage ovarian follicle tracking by ultrasound was not yet developed hence patients had to be in hospital for several days in the periovulatory period for intense hormonal monitoring with a coarse bioassay with wide co-efficients of intra- and inter-assay variation. In my own unit with Professor Craft, we utilized a similar system and also began to avoid the frustration of admitting women with defective cycles by developing ovarian monitoring on B-mode scanning, around the time of the pioneer reports by Hackeloer. Even so, the exercise of chasing the single oocyte from natural cycles was enormously frustrating for patients and researchers. On 8-hourly HiGonavis testing we might detect the LH surge but we were often way out in our estimate of its onset. We soon decided that IVF would not become a viable treatment mode in this way and began to research our own ideas on cycle stimulation as well as the aspect of luteal support treatments. I preferred the use of hCG injections (after Swyer) to maintain the luteal phase and this certainly worked well in clomiphene stimulated cycles, but led to increased ovarian hyperstimulation syndrome (OHSS) in gonadotrophin cycles (about 5%); hence a more complex biphasic model has been developed in my current program in Australia at the IVF Center known as PIVET. Although the first 2 infants in the UK and the first Australian infant (Candice Reed, Melbourne 1980) arose from natural cycles, it were stimulated cycles which have generated almost all of the further estimated 250,000 IVF pregnancies in the world!”

“The egg collection must also have been a problem.”

“At that time we undertook egg collections using a laparoscopic technique. That meant general anesthesia and the need for hospitalization and access to operating theatres. You can imagine the difficulty of accessing operating lists in NHS hospitals on lists not allocated to you on days dictated by vagaries of the ovarian cycle, even weekends and often bizarre times of the night dictated by our calculation of 34 hours from estimated onset of the LH surge!! Professor Craft and I found the obstetric unit and delivery suite at the Royal Free Hospital in Hampstead, London a thankfully obliging home for the IVF program at that time. We started using Steptoe’s Y-tube finger-suction method and various single lumen needles, but I soon started to explore a foot-pedal controlled aspiration system and later double lumen needles which allowed concomitant follicle flushing. In a paper I presented at one of the early IVF Congresses, I indicated that the optimization of laparoscopic oocyte recovery was dependent upon 3 main factors: Timing factors relating to the ovarian stimulation schedule, onset of the LH surge or hCG trigger. The instrumentation (16 gauge
needle bore and dual lumen aspiration/flushing needle with specific bevel features preferred). Ovarian access (sometimes preliminary pelvic adhesiolysis and other pelvic preparation required).

There were other difficulties in those early days which you may not even believe. For example, the IVF program was my Ph.D. thesis project, meaning one often conducted every aspect of the work including patient preparation, HiGonavis testing, ultrasound scanning, laparoscopic oocyte recovery, oocyte identification from the aspirates, sperm preparation, laboratory aspects of fertilization, pronuclear stage dissection and the entire embryo transfer procedure as a solo act. We did achieve two failed first trimester pregnancies in 1979 using natural cycles but soon Professor Craft, from London, and myself after returning to Perth in Western Australia reported many pregnancies from stimulated cycles. We could actually talk about pregnancy “rates” by 1982!

Dr. Hugo Verhoeven: “So ovulation induction and timing of the egg retrieval was the first breakthrough and the first key to your success.”

Dr. John Yovich: “Hugo, you visited my clinic in its early days but do you know why it is called PIVET?”

Dr. Hugo Verhoeven: “Actually, no.”

Dr. John Yovich: “PIVET is a sort of acronym for Programmed IVF and Embryo Transfer and shows my strong feelings about controlled ovarian stimulation. In fact, Hugo, as you know Jeanne and I have now been married for well over 30 years, but that period of time when I was chasing natural cycle collections was very taxing on our relationship. I am not so certain that our marriage would have survived if I had not developed a more organized programmed egg collection system where we could undertake egg collections at a regular time on morning operating lists.”

Dr. John Yovich: “But at this moment the pregnancy rates were still quite low so tell me: how many patients did you have to treat for having one pregnancy, was your pregnancy rate 3%, 4%, 5% - how high was it?”

Dr. John Yovich: “This is also quite an interesting story because each pregnancy in those days, the early eighties, was a celebration with champagne. My first successful pregnancy arose in a series of 42 laparoscopic egg pickups so that was a 2.5% pregnancy rate. That young boy is now a healthy young man of about 19 years, who manages a family farm in our SouthWest. The early pregnancies seem to have been rather special and many of them who are now in their mid to late teenage years visit the PIVET Medical Center for a drop-in chat and morning tea on very regular occasions. Many of them remain interested in IVF and come to see us for information to prepare their assignments for high school and university. As I mentioned, the first baby born in Australia was Candice Reed; she was born in Melbourne and is of interest because it details another important historical story. You may not be aware but Professor Carl Wood had been researching IVF for over a decade in Melbourne. After the birth of Louise Brown, the Melbourne program became divided with Ian Johnson (gynecologist) and Alex Lopata (scientist) transferring operations to the Royal Women’s Hospital – they pursued the natural cycle technique. Candice Reed arises out of that particular program but of special interest is that I can recall them undertaking a least a further 180 laparoscopic egg collections without a further pregnancy! At the Monash Unit, centered at that time at the Queen Victoria Hospital in Melbourne, Carl Wood continued the program with Alan Trounson utilizing ovarian stimulation. That program began to generate pregnancies a few months after Candice Reed, and in fact documents the first respectable “pregnancy rate”, which I recall was somewhere around 14% or 15% in the years 1982 to 1984. Our program in Perth generated a pregnancy rate of around 12% during that time.”

Dr. Hugo Verhoeven: “What was the next breakthrough that ended in a better success rate?”

Dr. John Yovich: “As I have said Hugo, by 1984 a number of programs around the world began talking about pregnancy rates, generally around 12% to 15%, units established in the United States and Europe as well as Australia and Britain. The units reporting such pregnancy rates all utilized ovarian stimulation of one form or another – most of the American units were using hMG alone whereas in Britain and
Australia we were utilizing clomiphene and clomiphene/hMG. Each of us was generally utilizing luteal support in the form of either progesterone or hCG injections, and sometimes a combination of the two. Of further interest, we were each exploring our own ideas on techniques of egg collection and techniques of embryo transfer, with a very wide array of equipment being generated at that time. During the early eighties advanced rapid immuno-assay methods became available so that oestradiol and progesterone levels, as well as the detection of the LH surge became more feasible. In fact, in the early eighties one of the major problems we faced was premature LH surges, so that many cycles resulted in collections at unscheduled times or actually cancelled altogether. Some clinics reported cancellation rates of the order of 15-20%. A further problem was that some patients had high basal levels of LH and often these levels became worse under clomiphene stimulation. Certainly the finding that continuous GnRH created pituitary down regulation and the subsequent introduction of GnRH agonists really helped to resolve these problems, enabling full follicular maturation without the fear of LH surges cutting the process short. Prior to that time, and once we had recognized the adverse effects of high basal levels of LH, many of my own patients were converted to hMG stimulation alone, and we utilized a 6-day rule concept, i.e.: giving the hCG trigger on the 6th day of significant oestradiol rise. In looking back I believe the reason we were able to report reasonable consistent pregnancy rates through the eighties related mainly to strict application of the 6-day rule and the use of good quality hormonal assaying on a daily basis. Those assays became even better with the subsequent introduction of immuno-assay methods.

A further benefit was the improvement in ultrasound equipment, initially moving from the static B-mode pictures to grey scale imaging and then electronically driven phased array probes which enabled real time imaging. The resolution of ultrasound images improved dramatically through the eighties and many clinics began to utilize ultrasound follicle tracking as the main method of determining when to trigger. In my own program we utilized both systems but remained reliant on hormonal assays as the stronger indicator until GnRH analogues became universally applied by the end of the eighties. Thereafter the question of detecting progesterone rises and LH levels became less significant and one could concentrate more on follicle dimensions, when the variations in his method became tightly reproducible.

A further problem we faced was that due to sperm deficiencies. Of course, if there was very severe oligospermia or azoospermia, couples were being directed into the donor sperm program. However, in normal IVF we knew that 50,000-100,000 sperm placed around the egg were sufficient to generate good fertilization rates. But the interesting finding which emerged was that if those 50,000-100,000 sperm came from a man with oligospermia, particularly if there was associated asthenospermia and teratospermia, then the sperm sample, although seemingly sufficient, would result in a very low fertilization rate and often failed fertilization. This then led to a lot of work to find some test of sperm function other than counting the numbers of motile spermatozoa with normal appearance. Such tests did emerge in the form of hemi zona binding, hyperosmolar swelling and acrosome reaction studies, particularly when these were ionophose/induced. Sometimes failed fertilization ensued even when sperm counts appeared perfectly normal beforehand, and again, sperm function tests could sometimes reveal such a likelihood. However, from the mid eighties, in my own unit we explored the use of pentoxifylline to enhance sperm function, sperm motility and the acrosome reaction with good effect in many, many cases, although we were still unable to resolve most of the cases with very severe oligospermia; i.e.: less than one million motile spermatozoa.

Another factor, which I think varied between units, related to the technique of embryo transfer. You will recall that Ricardo Asch introduced the GIFT procedure in about 1984. At PIVET we went a step further and compared the transfer of not only gametes, but pronuclear oocytes (PROST; pronuclear stage tubal transfer) and cleaving embryos (TEST; tubal embryo stage transfer). This showed a significantly higher, embryo implantation rate for tubal transfer over uterine transfer! In the late eighties, using the tubal transfer techniques we were reporting pregnancy rates consistently around 35% utilizing the tubal transfer method. However this made us relook at the uterine transfer technique, and I would now believe that many embryos in the earlier days were good embryos but poorly transferred, even, I must now admit, in my own hands. What we then moved to doing in the past 10 years, is to utilize the softest possible catheter (e.g.: Wallace catheter or K-Soft or similar), and transfer under ultrasound control where we utilize a full bladder technique such that the cervical canal and uterine canal are in alignment enabling a very easy uterine transfer, and ultrasound confirmation of the bright echo confirming an appropriate transfer location 1cm short of the uterine fundus. We reduced the transfer volumes down from 30 to 50 uL to as little as 5 to 8 uL with immediate significant benefit.
Another significant revolution going on in the IVF field was the conversion from laparoscopic egg recovery to ultrasound directed techniques, initially trans vesical, then trans urethral and finally trans vaginal. There were numerous benefits to this system including the higher egg recovery rate, less traumatic egg collection, the feasibility of collecting without general anesthesia or major anesthesia and, as colleagues such as Hamburger and Feichtinger showed around 1984, women did not need to go into a hospital setting for IVF procedures. This meant that clinics could be set up as free standing units without exposure to anaesthetic drugs and other sterilizing substances (e.g.: glutaraldehyde fumes) found in hospital and theatre settings. In my own program when we moved out of the hospital into the PIVET Medical Center, and our ambulatory clinic environment, the pregnancy rates escalated and remained much more stable than they had ever been before. Associated with this change was a greater simplification of the overall IVF procedure, and I believe patients tolerated the treatments and procedures far better without the daunting and formal process of hospital admissions, commitment of hospital bed and general atmosphere of being in a place for sick people. The ambulatory system available in infertility clinics created a much greater demystification of the process and general comfort and confidence for its patients. This has also enabled husbands to be more closely involved with their wives during egg collection procedures and embryo transfers. As I was indicating earlier, more attention to the embryo transfer technique in such ambulatory settings, caused the previous statistical difference between implantation rates in tubal transfers and uterine transfers to disappear. Nowadays we only undertake tubal transfer for situations where there is technical difficulty undertaking a trans cervical uterine ET for anatomical reasons.

Dr. Hugo Verhoeven:

“So what was the effect of those sensational developments on pregnancy rates?”

Dr. John Yovich:

“Hugo, by 1990 advanced units were reporting overall pregnancy rates of around 25-30% per treatment cycle. Furthermore, cryopreservation programs were becoming quite sophisticated and the development of IVF meant that the majority of patients were now having additional embryos cryopreserved. Clinics were beginning to look at their younger good responder patients and indicate that a single egg collection, followed by two frozen embryo transfer procedures, could generate pregnancy rates around 50% or higher. However, as you know the additional problems of ovarian hyperstimulation syndrome and multiple pregnancies were certainly beginning to emerge in large numbers by that time causing major public concern.”

Dr. Hugo Verhoeven:

“What are the important developments of the last decade?”

Dr. John Yovich:

“Hugo, the main development of the past decade has been the introduction of the ICSI technique. Many of us were exploring micro manipulation methods to enhance fertilization in men with sperm disorders throughout the latter part of the eighties. We used zona splitting techniques, including partial zona dissection as well as sub zonal insemination. A few pregnancies were generated from those techniques, but once we started to look at MESA (i.e.; micro epididymal sperm aspiration) we found those techniques to be virtually useless. However, the ICSI method whereby a single prepared sperm was injected directly into the cytoplasm of the oocyte, proved to be very successful and reproducible. We are so impressed with this method that it has enabled a wide array of male factor etiology and fertility to be treated, even to the point of collecting sperm from some men with Klinefelter’s syndrome who have very small testes (approximately 5.0 ml volumes); but occasionally a few sperm can be recovered from the testes and utilizing the ICSI technique occasional pregnancies have been reported. This means that nowadays ICSI enables treatment of oligospermic men, men with sperm dysfunctions as well as men with azoospermia, whether this is because of obstructive reasons or because of maturational arrest or spermatogenic failure. It is true that some of the latter cases do not reveal sperm and still require consideration of donor insemination treatment, but such programs these days involve very few cases of male factor infertility, and in Australia the main access to donor insemination programs nowadays is proving to be from single women! This is a dramatic change from the situation only 10 years ago.”

Dr. Hugo Verhoeven:

“What about the laboratory, what did change here since the early days?”

Dr. John Yovich:

“Hugo, what we learnt during the eighties was that the lab techniques described by colleagues...”
such as Chang, McLaren, Biggers and Whittingham, for animal work, applied very well for the human situation; in fact human IVF proved to be a lot simpler than that from many animal species. Nonetheless, what we really learnt in the eighties was to be very strict in controlling essential laboratory criteria of pH and osmolality of culture solutions and temperature aspects with respect to the culture media and gamete exposure. So the basic culture techniques did not change, but our attention to the low tolerance in the systems was gradually realized. This meant more attention to water quality, which is the main ingredient of culture media, the osmolality of which needs to be precisely controlled, and the pH of various media including flushing media, handling media, culture media and cryopreservation media, with the use of appropriate buffers. Above all however, we learnt to precisely control the temperature requirement, particularly when Pickering demonstrated how readily the meiotic spindles of oocytes were disrupted by dropping the temperature by as little as 2oC. This meant microscope stage warmers and bench warmers and incubators with minimal fluctuations became important and were developed.

So too did we realize that oocytes at 34 hours post hCG were not fully ready for fertilization. Initially this was corrected by delaying the insemination time to around 4 to 6 hours post oocyte recovery. Nowadays we extend the collection time to around 36 to 38 hours post hCG trigger, and check oocyte maturation; looking for M-II oocytes or allowing a few hours for M-I oocytes to mature up in vitro prior to insemination.

Further advances in the laboratory included the use of the assisted hatching technique and subsequently the evolution of blastocyst culture with the development of appropriate culture media to enable that. In certain cases where sufficient embryos allow for blastocyst culture, this means better embryo selection and a higher embryo implantation rate, so that we are now closer to the one embryo transfer stage and still maintaining a chance of pregnancy of around 40-50%. Blastocyst culture is generally combined with a technique of assisted hatching, whereby the zona is partially lysed by acid Tyrode’s medium or a laser technique. Whilst it seems not to be so important for the majority of IVF cases, assisted hatching of oocytes at the 4-8 cell stages does appear to confer benefits for older women, those who have demonstrated repeated failure to implant and possibly for frozen embryos.

Dr. Hugo Verhoeven: “Are still further improvements likely in the standard IVF technique?”

Dr. John Yovich: “As I have indicated before, the current technique provides a reasonably high pregnancy rate for younger patients (i.e.: under 35 years) who are good responders to stimulation. However, there are sub groups of difficult cases such as the poor responder female, in whom we are trying to find better methods of stimulation. In this sense it appears that some women demonstrate direct ovarian suppression with the GnRH agonists, and this might become avoidable with the use of the antagonists which can be used later in the follicular phase simply to block the LH surge. There is also the current development with azoospermic men who have spermatogenic failure, whereby in vitro sperm maturation is beginning to emerge as a potential therapeutic mode for those cases.

Similarly, from the female aspect, older women and sometimes younger cases produce oocytes which appear to lack the full potential for embryo development. In that situation some work we and others have been exploring is the use of cytoplasmic or ooplasmic transfer. It does appear that a small amount of cytoplasm taken from high quality donor oocytes can “rejuvenate” aged or poor quality oocytes. So far there are few pregnancies from this technique, but it may well provide a future benefit in cases where the only solution at present is to use entire donor oocytes.

Of course, in the early days we were obsessed with the idea of generating reasonable pregnancy rates from IVF treatments, but we have become increasingly concerned with the condition of OHSS, that is the severe forms of ovarian hyperstimulation syndrome, with the attendant ascites compromising respiration and creating hypovolaemia with attendant risks of thromboembolic phenomena. Of course various strategies have evolved to minimize this risk and to treat it effectively; but ideally, because it is entirely an iatrogenic condition, we would like to avoid it altogether. To this end we are putting considerable effort into developing the technique of IVM, that is in vitro maturation of oocytes, in two models – firstly collecting oocytes from early antral follicles in polycystic ovary cases without the use of any stimulation. In fact these are the patients who are most at risk of developing severe OHSS, and it is pleasing that several groups have generated pregnancy rates of around 25% in such cases, although the overall fertilization rate of such oocytes.
remains low. The other situation for IVM involves maturation of follicles from ovarian biopsy specimens, which have usually been cryopreserved some months or even years prior. This is a very interesting model as it raises the possibility that women may put some of their ovary tissue into cryopreservation whilst they are still young, for example in their mid to late twenties, with a view of IVM a decade or so later when they are ready to conceive. So far this remains a theoretical possibility, as I am not yet aware of any successful pregnancies from the technique. In our own work we have found that whilst nuclear maturation seems to occur reasonably normally, there are some deficiencies in cytoplasmic maturation. Where we have used ooplasmic or cytoplasmic transfer into such oocytes, we have had improved outcomes in the animal models. This may well prove to be the case for the human situation as well. Certainly if we could work with women in the infertility setting without having to stimulate their ovaries, I believe this will become a far more acceptable methodology of IVF from the perspective of both patients and the medical staff."

"Do you think that it will be possible in the near future to inject chromosomes out of other body cells instead of sperm cells. Will it be possible to inject chromosomes out of an hepatic cell directly into the oocyte with a pregnancy as a result?"

"Hugo, just before we get into that esoteric side, let me just put another practical side to IVF as it links up to other developments in surgery of the reproductive system. The IVF revolution, which has only been 20 years, has taught us so much. As I indicated earlier, it was brought in as a technique to resolve infertility due to tubal obstruction, but you and I are both microsurgeons who continue to try and resolve tubal infertility by improved techniques which have led on to another revolution in the area of endoscopic surgery. We tried to resolve this factor by doing extremely technically demanding reconstructive work, and we achieved a number of pregnancies, but IVF has achieved many, many more. What actually happened was that in the mid eighties we started to explore the idea of using IVF in non-tubal types of infertility. We found that it could actually resolve infertility for many other types of conditions, some of which we know about like endometriosis, male factor infertility, presence of antisperm antibodies and a whole array of fertility disorders. Whereas microsurgery had improved but limited results, endoscopic surgery has taken you and me out of microsurgery into laparoscopic surgery, and I believe that as the two areas have evolved together there are co-benefits. For example, we have improved the outcome of IVF for patients with severe types of endometriosis by undertaking preliminary clearing of the endometriosis using effective laparoscopic techniques. In addition, the more recent data shows that laparoscopic myomectomy can improve the outcome of IVF for patients with fibroids, and the clearest data shows that laparoscopic pelvic tidy up surgery, including the removal of hydrosalpinges improves IVF outcomes for those patients. In my own clinic we are putting together quite a lot of data at the moment, auditing the work we have done on pelvic endometriosis. Certainly we have shown dramatically improved outcomes for IVF in that group by clearing the adenomyosis and endometriotic lesions beforehand; but what we have also begun to notice is that the more effective types of laparoscopic pelvic surgery for infertility conditions, such as clearing endometriosis, has led to a significantly higher rate of spontaneous pregnancies in patients awaiting IVF. In the PIVET program we generate about 500 pregnancies a year, but the proportion of patients conceiving spontaneously now after preliminary endoscopic workup and preparation is increasing quite dramatically, and others are proving quite suitable for simple IUI treatment rather than the more invasive procedure of IVF. Therefore I believe that infertility clinics should be paying attention to the development of both IVF and endoscopic surgery, in order to provide the best outcomes for their patients.

Now to get back to your question, Hugo, concerning chromosome or nuclear transfer, perhaps from somatic cells, I believe there are two areas which are relevant to discussion in this context, i.e.: the technique of cloning and the technique of stem cell culture. It is the evolution of IVF technology which allows us to even consider these approaches to resolving medical disorders. As you know the technique of cloning involves taking the nucleus from a somatic cell and fusing it with an activated oocyte, which has had its own nuclear material removed. This means you can propagate offspring with chromosomal identity matching that of the nuclear (chromosome) donor which might be another living animal or human being. Certainly that put fear into the general community and ethicists have tended to ban the concept of propagating humans in this way. However, if the cloning concept is teamed up with the stem cell culture idea, I believe this will be a very useful technique to assist in dramatic changes to medical therapies for severe conditions. As you know stem cells from
early embryos have the potential to differentiate into a wide array of tissues. If one uses a cloning technique to develop an embryo whose stem cells are then harvested and thereafter induced to form new tissue cells, such as new liver cells, brain cells, pancreatic islet cells or the cells of other organs, this could lead to the transfer of those cells into the nuclear donor who might well be able to have new liver or kidney cells transferred to correct liver or renal failure; or substantia nigra cells to correct Parkinson’s disease disorder, or neuronal cells to correct for Alzheimer’s disease, or pancreatic islet cells to correct for diabetes or stem blood cells to correct leukemia and aplastic anemia, or any other organ failure condition. So far the techniques of inducing stem cells to develop down a particular line of differentiation are in the early phase of laboratory development, but if we take away the fear of cloning and provide its utility in the stem cell culture model, then the human race will have a very powerful therapeutic tool indeed.”

“So, my final question. I did not interrupt you that many times as I was fascinated by just listening to your story. Is there anything you did in the field of IVF, that you regret now? Are there any steps that maybe were a step too far. For the future, is there any treatment possibility you could say: “That I wouldn’t do even if the technology would be available”, for instance sex selection?”

“I think that is a very interesting question that you asked Hugo. I do not regret any aspect of the evolution of IVF, but I believe we have only just got past the first stage of a wonderful future which arises out of IVF research. From the foregoing discussion it can be seen that the main incentive was to help resolve the anguish of infertility; but in truth many of us believed that the patients presenting with infertility gave us an opportunity to explore the very foundations of human reproduction, about which knowledge by the early seventies was simplistic and mysterious. Certainly we have resolved the infertility question for many couples and this question is an increasingly important one in our evolving society. But further to that, it allowed us to explore basic embryology, molecular and cellular physiology and precisely how the genetic aspects apply in the human situation. We now know that the reproductive process was far more complex than initially presented; certainly much more complex than the basic teaching you and I had at medical school in the sixties. I particularly like the fact that as we set up our infertility clinics such as the PIVET Medical Center, we incorporated dedicated doctors, nurses, laboratory staff, ultrasonographers, psychological counselors, genetic counselors and administrative staff all within a tightly working team. In my own center sub groups meet each week and the entire group meets once a month to discuss management aspects and future directions for the clinic. Research activities go on continuously and many of these are in collaboration with universities and other centers. This aspect of teamwork and medicine in an interesting medical area creates a very exciting and rewarding working environment. So too is the challenge of preparing all new protocols for approval by our institutional Ethics Committee and trying then to work within the community and legislation which has been introduced to control our activities. Nonetheless there have been some disappointments, particularly where we have failed some patients, more so in the earlier years, and it still remains a major concern for me when a healthy young woman develops severe OHSS as a consequence of our ovarian stimulation therapy. So fortunately, I think in recent days we began to realize that many of those patients who did develop thromboembolic conditions actually have an underlying thrombophilia tendency. In my own unit, we have introduced routine thrombophilia screening and detected quite a number of cases with abnormalities such as homocysteine elevations and Factor V Leyden deficiency. Such patients now receive prophylactic Aspirin and Heparin where indicated. With respect to questions like surrogacy, sex selection and IVF for single women, I am personally happy to treat all those situations, but I do believe that these need consideration by the community as they are issues for society to debate. For example, some European countries regard IVF as a very important mode to help maintain birth rates in general. In my center we do assist single women to have pregnancies but the counseling issue becomes very important, and currently our community is debating their attitudes to this, and in particular specifying their attitudes with respect to heterosexual and homosexual single women. And sex selection provides another aspect of interest, as there has been a fear that some communities would specifically select for male infants. But in truth, the requests received around Australia indicate a fairly even balance of requests, perhaps slightly more for female infants. I have even read a recent report indicating that Japanese women are increasingly requesting sex selection for female infants.

In 1986 I helped two women with absent uterus (one congenital and the other post hysterectomy)
achieve surrogacy pregnancies using their own oocytes and their respective sisters carrying the embryos. However I received a backlash of criticism from a fearful community, but I can indicate that the resulting children now aged in their early teens are happy and healthy, so far not displaying any identity confusion problems. In fact, the same community has now recently approved the principal of IVF surrogacy in the setting of what I previously termed compassionate family surrogacy.

Overall then Hugo, I do not regret any aspect of the work we have applied in developing IVF to its current stage. The future for medicine in general is now very exciting from this current base but it does require the scientific and medical communities presenting it’s plans to the general community for debate and interaction to achieve the optimal progress into the future.”

**Dr. Hugo Verhoeven:** “John, thank you very much, it was a real pleasure.”

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