assisted reproduction technology in men with ejaculatory dysfunction with special reference to spinal cord injury. Doctoral thesis, Karolinska Institute 1998. Claes Hultlin, Spinalis

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This thesis stems from the Department of Surgical Science, Section of Rehabilitation Medicine at the

Karolinska Institute, Stockholm, Sweden. It deals with the demanding sequela of infertility in men with

spinal cord injury (SCI) or testicular cancer (TC) treated by retroperitoneal lymph node dissection

(RPLND).

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AIMS OF THE STUDY

- To evaluate the effectiveness of advanced forms of assisted reproduction technology (ART), in men with SCI suffering infertility, with particular reference to intracytoplasmic sperm injection (ICSI), and compare it with previously published results using simpler methods.

- To evaluate the use of in vitro fertilization (IVF) /ICSI in men with anejaculatory infertility after RPLND for TC.

- To investigate if spermatogenesis in men with meningomyelocele (MMC) is sufficient for ART

- To investigate if risks of autonomic dysreflexia and other complications during electroejaculation (EEJ) in general anaesthesia (GA) are justifiable with regard to the purpose of the treatment.

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ABBREVIATIONS

AC	Alternating Current
AD	Autonomic Dysreflexia
AID	Artificial Insemination with Donor sperm
ART	Assisted Reproduction Technology
ASIA	American Spinal Injury Association
AVM	Arterio Venous Malformation
COH	Controlled Ovarian Hyperstimulation
DC	Direct Current
ED	Ejaculatory Dysfunction
EEJ	Electro Ejaculation
ET	Embryo Transfer
FER	Frozen thawed Embryo Replacement
FR	Fertility Rate
FSH	Follicle Stimulating Hormone
GA	General Anaesthesia
GIFT	Gamete Intra Fallopian Transfer
Gn	Gonadotropin
GnRHa	Gonadotropin Releasing Hormone agonist
hCG	human Chorionic Gonadotropin
HLA	Human Leucocyte Antigen
HPG	Hypothalamic-Pituitary-Gonadal axis
ICSI	Intra Cytoplasmic Sperm Injection
IUI	Intra Uterine Insemination
IVF	In Vitro Fertilization
LH	Luteinising Hormone
MMC	Myelo Meningo Cele
NSGCT	Non Seminomatous Germ Cell Tumor
OPU	Oocyte Pick-Up
PVC	Poly Vinyl Chloride
PVS	Penile Vibratory Stimulation
RPLND	Retro-Peritoneal Lymph Node Dissection
SCI	Spinal Cord Injury
TC	Testicular Cancer
TESA	Testicular Sperm Aspiration (by the percutaneous route)
TESE	Testicular Sperm Extraction (from open biopsy material)
WHO ICIDH	WHO International Classification of Impairments, Disabilities and Handicap
ZIFT	Zygote Intra Fallopian Transfer

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1. INTRODUCTION

Until just after World War II, SCI usually was a rapidly lethal condition (Guttmann, 1976). Up until that time, rehabilitative aspects of SCI was therefore not an issue. Sir Ludwig Guttmann, the undisputed mentor of modern SCI treatment, introduced a new treatment paradigm, that led to a dramatic improvement of the prognosis *quo ad vitam.* With patients surviving, issues pertaining to physical and psycho-social readjustment came into focus. Thus, during the last five decades, emphasis has shifted from mere life-supporting measures to enhancement of quality of life.

Testicular cancer (TC), was likewise a lethal condition until the late seventies (Klein and Kay, 1993). With this perspective in mind, problems like infertility were not on the agenda. With modern comprehensive medical and surgical care, life expectancy in this group has improved dramatically. Today over 90% of men with TC have an expected life span that approaches that of the normal population (Donohue et al, 1990; Presti et al, 1993).

The urge to become a father and to secure the family succession is one of the most basic instincts in every species, man included. It is therefore not surprising that one of the major concerns for men suffering trauma or disease is impairment of the reproductive function (Gray, 1993).

For decades, sterility was a fate that most men surviving SCI had to accept (Bodner, 1993) as was the case for men surviving TC/RPLND (Klein and Kay, 1993). Limited attention was given to this problem and patients were often told not to have any expectations (Bedbrook, 1981). With the recent availability of effective assisted reproduction technology (ART), it should now be mandatory to include a fertility service in the rehabilitation program.

According to the WHO classification (WHO International Classification of Impairments, Disabilities and Handicaps, 1980) it is clearly stated that "the impairment concept refers to any loss or abnormality at the

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organ level. It includes both temporary and permanent defects, anomalies and dysfunction". Disability is defined as "a restriction of an individual's ability in terms of functional performance and activity as a result from the impairment, e. g. eating and dressing, or intercourse and parenthood. Handicap, then, is concerned with a disadvantage experienced by the individual, resulting from an impairment or a disability. Thus it reflects an interaction with and adaptation to the individual surroundings". Disturbed sexual function will have an impact on all three levels, although to a varying extent, depending on age, extent of injury, personality and life-style of the affected individual.

Every year a large number of active young persons suffer SCI around the world. The incidence of SCI ranges from 9 per million and year in Sweden (Swedish National Board of Health and Welfare, 1995) to 100 per million and year in Thailand (Meinecke, 1990). The majority of SCI patients are men, most reports quote 80-85% (Lee et al, 1991).

In the rehabilitation process treating SCI men, everyone agree on the fact that sex and fertility are important (Comarr, 1970). It should be as natural for a newly injured patient to receive full and adequate information regarding these problems, as practising dressing, car driving or tooth brushing. Sadly, this is still not the case (Nordqvist, 1988).

The rehabilitation process aims towards enabling a person with a disability to recover physically, socially, mentally and economically. A successful rehabilitation implies that the work conducted together with the team reduces handicap and social limitations so that the person achieves maximum quality of life. Knowledge of a person's fertility status is vital in this process (personal experience).

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1.1 Sex and fertility

Masters and Johnson (1988) describes three rationales for having sex: Procreational, i.e. for having children; recreational, i.e. for having fun with no other goal; and relational, i.e. for sharing with a cared-for person. This thesis deals primarily with sexuality in the procreational context. However, since sex and fertility are firmly linked together, it becomes important to sort out some aspects of sex for this category of patients.

Sexuality means different things to different people. It can include love, arousal and a way to avoid loneliness. It involves positive feelings most of the time, but may also cause a lot of frustration. Sexuality is an important component in the life of most human beings. If a person does not experience physical sexuality him/herself regularly, he/she nevertheless thinks of sex and has sex fantasies as a natural part of daily living (Kaplan, 1974). Disabled persons in general have the same urge for sex as able-bodied individuals. Most men with SCI suffer sexual dysfunction, mainly as erectile dysfunction (Jequier, 1986). The impact will thus not be restricted to procreational difficulties, but will also influence the other aspects of sexuality.

As a consequence of the female emancipation and more equal marriages, in combination with contraceptives, women have more opportunities to live out their sexuality. The traditional concept of the sexually active man and the sexually passive woman is changing and this has improved the situation for disabled men in regard to sexual experiences. Thus, it is easier for a paralysed man to accept a less dominant role in a sexual relationship. A successful adaptation process is characterised by such a re-orientation, whereas failure to adapt leads to constant frustration or passive acceptance with maladaptive psychological defence mechanisms. This is often noticed by the chronically ill becoming regressively

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dependent on others, particularly the partner. He can become depressed and passive with low self-confidence and he also feels stigmatised (Fugl-Meyer and Fugl-Meyer, 1994).

1.2 Sexual dysfunction after spinal cord injury

Most men with a SCI suffer from sexual dysfunction, mainly due to erectile and ejaculatory dysfunction. The Stockholm Spinal Cord Injury Study shows that 30% of the male patients had not had intercourse after the injury (Levi 1996).

Penile erection is dependent largely upon the sacral parasympathetic nerves, whereas emission of semen is relayed through the sympathetic nerves (Andersson and Wagner, 1995). In spinal shock, in the acute stage after SCI, erectile and ejaculatory function are usually absent. After spinal shock has subsided, these men may experience different types of erections, depending on the type and level of injury:

- Reflex erection is an erectile response after mechanical stimulation and is only present if there is an upper motor neuron lesion.

- Psychogenic erection can be achieved in about 25% of the lower motor neuron lesions (Smith and Bodner, 1993) and usually no reflex erection is obtained in this group of patients.

It should be realised that neither of these erections are as long-lasting as those in men without neurogenic sexual dysfunction and may subside prematurely. This implies that the erection usually declines after a short time during intercourse and therefore needs support.

1.3 Sexual dysfunction after testicular cancer

TC is the most frequent type of cancer affecting men between the age of 20 and 40 years of age. Since the early 1970's there has been an annual increase in incidence in TC of 2.8% in Sweden.

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TC has an incidence of about 1% of all neoplastic diseases affecting men in Sweden. The present age-adjusted incidence of TC in Sweden is 44 new cases per million men and year (National Board of Health and Welfare, 1996). In the age interval 15-40 years TC is the most common malignant tumour (Klein and Kay, 1993). Sexual dysfunction after treatment including retroperitoneal lymph node dissection (RPLND) occurs in about half of the cases (van Basten et al, 1997). It is more common with ejaculatory than erectile dysfunction after RPLND. If the T10 and L1 sympathetic nerves, or the S2/S4 parasympathetic pathways and the somatic afferent nerves have been affected by the surgery, the sexual capability is impaired (Klein and Kay, 1993).

1.4 Erectile dysfunction

Erectile dysfunction in men with SCI and TC with RPLND both belong to the group of neurogenic sexual dysfunction. As a rule treatment can be initiated without prior diagnostic intervention, i.e. psychosocial factors, male sex hormones and penile acceleration ratio do not need to be explored routinely.

The basic way to deal with erectile dysfunction is to find a way to support the reflexogenic erection. The least invasive and simplest approach is to use a broad rubber band or a pubic ring which should be placed at the base of the penis. If the penis is erect when trying to apply the pubic ring, there is a risk that the manipulation leads to a loss of the erection. Therefore it is better if the pubic ring is mounted onto a tube or a vacuum pump before being applied onto the base of the penis (Biering-Sörensen and Sönksen, 1992).

The vacuum pump is a device that evacuates the air from inside a rigid sheath around the penis. After application of some degree of vacuum, the rigidity of the penis becomes sufficient and the pubic ring can be transferred from the sheath of the pump to the penis. In many cases this makes the erection last long

enough in order to perform coitus. The tension of the rubber band or the pubic ring should be adjusted according to the diameter of the penis shaft. This technique often causes the penis to change colour to pale and it becomes cold. A disadvantage of this technique is that the base of the corpora cavernosa is not encompassed by the treatment, which leads to a very unstable penis. This should be considered during the sexual act.

Intra-cavernous pharmacotherapy has become very popular during the last ten years (Ducharme and Gill, 1997). The drug is injected into the corpora cavernosa at the middle of the penis shaft. Papaverine has been used for several years in a standard dose of 40 mg/injection. Today, prostaglandin E1 (Caverject®, Pharmacia Upjohn, Uppsala, Sweden) used in doses of 10-20 μg, has become the drug of choice for intra-cavernous pharmacotherapy. It is also considered less noxious to the tissue than papaverine (Olsson, 1994).

Priapism is a very rare side effect in SCI patients. Nevertheless, it is important to inform the patient that if the erection lasts for more than about 8 hours he should seek treatment. The antidote is efedrin and 25-50 mg should be injected into the corpora cavernosa. If that is not sufficient the physician has to evacuate blood from the corpora cavernosa, usually using a regular syringe needle.

A new orally administred vasodilator drug for treatment of erectile dysfunction is sildenafil (Viagra®, Pfizer, London, England), which is a selective inhibitor of phosphodiesterase type 5. It has been tested for SCI men in a large, double-blind, randomised, placebo-controlled multi-center study during 1996 and 1997 and proven effective and safe (Dinsmore et al, 1997).

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For a few patients the above-mentioned techniques are not sufficient, and if they want a good enough erection for penetration, they need to have penile implant.

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1.5 Ejaculatory dysfunction

The ejaculatory reflex *per se* is a complex event that can be inhibited or facilitated by local or central pathways (Bannister and Matthias, 1992). It should be understood that there is a difference between seminal emission and ejaculation. Seminal emission refers to the deposition of semen from the prostate, seminal vesicles, and distal vas deferens into the posterior urethra. This event precedes ejaculation. Ejaculation is the anterograde propulsion of semen through the penile meatus (Kvist, 1994). The efferent neural pathways arise from the spinal levels T10 to L2 and travel through the sympathetic chain ganglia, the hypogastric plexus anterior to the aorta and the pelvis to the prostate, vas deferens and seminal vesicles. It involves somatic efferent nerves through S2-S4 via nervus pudendus and autonomic nerves T12-L2 via nervus hypogastricus. The afferent sensory nerves are the dorsal nerves of the penis. In an able-bodied man the ejaculatory reflex is initiated by sensory stimulation of the penis and by cerebral erotic input. At the time of emission, other sympathetic fibers tighten the internal urinary bladder sphincter. This normally prevents retrograde ejaculation. (Kvist, 1994).

The process of ejaculation is separate from that of erection and from what is referred to as orgasm. These events usually occur within close proximity, but they are physiologically independent. Because of the fact that they usually occur together as a summation of sexual stimulation, they can enhance each other psychodynamically.

The intricate neurology of ejaculation can be disturbed by many factors, e.g. central or peripheral nerve damage, hormonal disorders, various drugs, psychopathological states et cetera. The men with traumatic SCI in this study, suffered ejaculatory dysfunction due to central or peripheral nerve damage, or a

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combination of both. The men with MMC usually suffered ejaculatory dysfunction due to peripheral (i.e. lower motor neuron) lesions, as did the TC/RPLND men.

Guttmann demonstrated in 1946 that intrathecal injection of prostigmin in doses of 0,25-0,30 mg was sufficient to elicit erection and ejaculation in traumatic para- and tetraplegics (Guttmann, 1949). In 1953 and 1960 he published the results of 134 patients injected this way, with lesion levels from C5 to S4. The results were by large good and most patients received erection as well as emission. In February of 1948, however, Guttmann lost one tetraplegic patient after an epileptic fit. The underlying cause was a cerebral haemorrhage. (Guttmann, 1976). This indicated that the method was rather risky. Because of this mishap, intrathecal prostigmin became less utilized and the infertility problem fell into oblivion.

Veterinary medicine has used electrical stimulation to achieve ejaculation since the 1930s (Nichols and Edgar, 1964). After World War II, such electrical stimulation was tried out on tetraplegic men and a pregnancy resulting from artificial insemination with sperm from such an ejaculate was reported for the first time in 1975. (Thomas et al, 1975)

The simplest way to achieve an ejaculate from a SCI man with an injury above T 10 is to use a vibrator. It is a successful method in the majority of patients (Sönksen et al, 1994). Sobrero described this for the first time in 1965 (Sobrero et al, 1965).

The French neurologist Francois performed 160 electroejaculation (EEJ) procedures, resulting in 63 ejaculates and also in the first child born after AIH (Artificial Insemination Husband) with sperm achieved through this technique (Francois, 1978). Brindley applied a modified EEJ technique to 84 patients, which resulted in anterograde and retrograde ejaculates in 50 subjects (Brindley, 1980). He also

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reported one pregnancy (Brindley, 1980). The EEJ techniques used by Francois and Brindley acted through direct current (DC), i .e. there was two anodes and one cathode that were mounted on either a set of rubber gloves or a plastic probe. The DC technique of Brindley differs from the alternating current (AC) technique developed by Seager in that the DC technique primarily stimulates sympathetic preganglionic fibers and the AC also stimulates the unmyelinated postganglionic fibers. In anejaculatory TC patients the technique *ad modum* Brindley is not effective, whereas the Seager technique is. This is because, after RPLND, the unmyelinated postganglionic fibers are still functioning (Brindley, 1981A). The Seager equipment, (Dalzell, USA, Medical Systems, Dungannon, N. Irland) is thus more effective and, furthermore, needs less operator skill (Halstead et al, 1987).

1.6 Infertility

In a general population, 10-15% of all couples will experience primary or secondary infertility some time during their reproductive life (Healy et al, 1994).
For most couples, having children is an essential part of the fulfillment of marriage. Indeed, the psychological reactions to the diagnosis of infertility are as severe as those to very severe life events (Andrews et al, 1992). Also, in many countries, childlessness has severe social and economical consequences. Male factors are estimated to be responsible for some 30% of cases of infertility, and contributory in another 20%. (Jequier, 1986; Howard, 1995). In SCI and TC men, neurogenic erectile and ejaculatory dysfunctions are the main causes of infertility, with impaired sperm function as a contributory factor.

In Sweden, more than 100 000 couples are involuntarily childless (Högberg, 1992). This type of disability is not socially acknowledged and it is difficult to share the experience with family and friends. Many couples deny their infertility and refrain from seeking treatment (Templeton et al, 1990). It reflects some

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of the most intimate parts in a relationship and puts a strain on the couple's sexual life. The bedroom becomes a place where performance according to the calendar becomes the key-element instead of the caring and loving atmosphere and spontaneity that most couples are striving for.

When treating infertile couples, it is important to acknowledge the psychosocial aspects. Also, it is adamant to treat the man and the woman as a functional unit and not as two separate individuals. A holistic approach is important in order to help the couple.

It is necessary that the couple receives full information about the investigations and the treatment. Both medical and psychological consequences should be discussed. This information should be conveyed orally at the first meeting and be supplemented with adequate written information.

Infertility in SCI men has a multifactional background. As has been pointed out, SCI commonly leads to both erectile and ejaculatory dysfunction, something which naturally impairs the ability to impregnate the woman through coitus. Additionally, sperm quality is usually affected.

The semen obtained by assisted ejaculation is characterised by high sperm counts but low sperm motility (Sönksen et al, 1996). However, the total motile count is most often above normal lower limits (20×10^6) (WHO, 1992). The validity of the WHO standard protocol for semen evaluation has been questioned (Helmerhorst et al, 1995; Ombelet et al, 1997). The sperm morphology is usually within the normal range (Denil et al, 1992; Chung et al, 1995). Etiologies for impaired sperm quality is yet to be determined. Several explanations for the affected semen quality have been proposed, such as recurrent UTI (Wolff et al, 1990), testicular hyperthermia, pro and con (Brindley, 1982; Brackett et al, 1994B), urinary contamination in cases of retrograde ejaculation (Hirch et al, 1992), long-term indwelling urethral catheters, stasis of seminal fluid (Ohl et al, 1992), changes in the hypothalamic-pituitary-testicular axis (Brackett et al, 1994) and changes in the biochemical constituents of ejaculates after EEJ (Hirsch et al,

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1991). Although the sperm quality generally does not correlate with level or completeness of injury, our experience is that azoospermia seems to be related to lesions engaging the T10 - T12 segment. Chapelle reports on T12-L2 being important neurological levels for normal trophic effects on testes (Chapelle et al, 1993). Thus, in the patient material at Spinalis, three out of four men with injury at T10 were azoospermic and the fourth had a total count of 7×10^6 sperm. This raises further questions about the role of the nervous system in the regulation of the spermatogenesis.

Infertility after TC/RPLND is likewise commonly due to multiple causes. Ejaculatory dysfunction precludes conception by intercourse. Additionally, most men with TC and treated with chemotherapy becomes azoospermatic two months after starting the treatment (Pont and Albrecht, 1997). The spermatogenesis may not recover until two years after chemotherapy (Padron et al, 1997). It is important that these men receive full information regarding the possibility of cryopreservation prior to surgery and chemotherapy, since there is no difference in post-thaw quality in sperms from men with TC compared with that of normal fertile men (Agarwal et al, 1995).

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2. PATIENTS

2.1 Papers I and III

All SCI patients treated for infertility have been recruited through the Spinalis SCI Unit at the Karolinska Hospital. Out of the 67 couples who approached Spinalis for infertility counselling, 31 were from the greater Stockholm area. The remaining 36 were from other parts of Sweden and from other countries. Twenty-five SCI men, reported in Paper III, had a median age of 34 years (range 25 - 51). They represented a neurologically heterogeneous group with SCI levels from C2 to L3. Complete injuries, i.e. ASIA Impairment Scale Grade A, dominated the group (18 of 25). The time since injury varied from three to 33 years. ASIA Motor Index Score (Ditunno et al 1994) ranged from 13 to 98.

The women were 21 to 38 (median age 31) years of age. Eighteen women were 0-gravidae and seven were gravidae I-II. Four women had children from previous relationships and one in the present relationship. Three women had undergone surgery for benign ovarian cysts and two women had polycystic ovaries. One of the women had been operated on for tubal adhesions and one woman suffered from multiple sclerosis.

2.3 Paper II

Ten men, median age 34 years (range 28 - 40), were treated for infertility with EEJ during GA and with IVF. All men had been treated for non-seminomatous germ cell tumours (NSGCT), and had undergone RPLND. The mean interval from orchidectomy was 10 years (5 - 14 years). Eight of the men had received chemotherapy due to positive lymph node relapse. Two of the men had proven fertility before their cancer

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treatment of which one in his present relationship. Serum follicle stimulating hormone (FSH) concentrations were normal in those examined (range 5 - 11 IU/l, n=6).

The ten women had a median age of 30 years (range 26 - 38) and all had regular menstruation periods. The findings on a routine gynaecological examination and pelvic ultrasonography were normal. Eight women were 0-gravidae and two were gravidae I-II. One women had a child in a present relationship and one women had been treated for salpingitis.

The patients were referred to the unit through the Department of Urology at Huddinge University Hospital and South Hospital in Stockholm.

2.4 Paper IV

All MMC men included in Paper IV had visited the Spinalis Outpatient Unit for an annual examination. Out of the 43 men visiting the unit between 1994 and 1996, nine expressed desire to have their semen analysed with the perspective of procreational capacity. These nine MMC men had a lesion level between T12 and L4, and ASIA score A to D. The median age was 27 years (range 22 - 39 years). All men were living in the greater Stockholm area. Their neurological lesion levels were established by clinical assessment of sensorimotor function according to ASIA standards. Five of the MMC men were confined to wheelchair and four could walk with the help of crutches or a walking stick.

2.5 Paper V

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Forty-five men underwent EEJ under GA at our unit from January 1991 till September 1997. Thirty of these were SCI men who needed anaesthesia in order to perform EEJ. The remaining 15 were anejaculatory due to TC with RPLND. The median age in the SCI group was 34 years (range 25-51) and in the TC group 35 years (range 28-40). The SCI group included 22 patients who had sustained SCI through trauma, seven congenital and one nontraumatic acquired lesion due to arterio-venous malformation (AVM). The ASIA Score in the SCI group ranged from A to D, and level of lesion from C4 to L3. Motor index varied from 13 to 98.

The TC group had a median age of 35 years (range 28 - 40). Fourteen had been treated for non-seminomatous germ cell tumors and one for seminoma. All had undergone RPLND and all but one had undergone orchidectomy and received chemotherapy. The histopathology of the primary tumours in the testicle varied, the most common being embryonal cell carcinoma and mixed germ cell cancer.

3. METHODS

3.1 Semen retrieval

3.1.1 Penile vibratory stimulation (PVS)

PVS aims to stimulate afferent fibres from the penis to the spinal cord and have the impulses relayed via reflex arcs to the efferent fibres controlling the ejaculatory mechanism (Sobrero et al, 1965). It was first performed in SCI men by Comar in 1970 (Comar, 1970). SCI men with a lesion level at T10 and below usually do not ejaculate with PVS. This is due to damage to nerve roots and sympathetic nuclei that control the ejaculatory reflex (Nehra et al, 1996). A large variety of vibrators have been used throughout

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the world (Brindley, 1981A). A home unit from Ferti Care (Multicept A/S, Rungsted, Denmark), has the advantage of adjustable amplitude and frequency (Sönksen et al, 1994), (Fig. 1). Good results are usually obtained with an amplitude of about 2.5 mm and a frequency of about 100 Hz. However, experience proves that any vibrator with enough impact usually serves the purpose well. Thus, as an example, one child in Sweden was born after home insemination where the man ejaculated after using an oscillating sanding machine (Black & Decker).

By narrowing the excitatory gap, physostigmin can be employed as an adjuvant to PVS (Chapelle, 1983). First, 10 mg of metoclopramide (Primperan[®], Tika, Lund, Sweden) is injected subcutaneously to counter some of the side-effects of physostigmin. Metoclopramide does not interact with the effect of physostigmin if injected 20 minutes beforehand. The physostigmin should be administred according to the weight of the patient, in a dose of 1-2 mg, 15 minutes prior to using the vibrator (Chapelle, 1983). If bradycardia occurs, 0,25 mg of atropin can be injected intravenously during the procedure. A significant proportion of patients who do not ejaculate with PVS alone, manages to produce semen after this procedure (see Fig. 3, page 95).

A previously undescribed way to extract semen, which may be useful in men with partially preserved innervation in the sacral dermatomes, is to expose the lower extremities to cold water. It was a serendipitous finding that some men with SCI experienced emission of semen when they were showering cold water on the lower parts of the legs and feet. One man reported that he ejaculated promptly when he put his foot into a bucket of ice-cold water. This patient has managed to become a father twice with semen retrieved by this "ice-cold-water-bucket-technique".

3.1.2 Electroejaculation (EEJ)

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If PVS with physostigmin does not elicit ejaculation, EEJ was then performed (Brindley, 1981B). We used a Seager Model 14 Electroejaculator (Fig. 2), (Dalzell USA Medical systems, Dungannon, N. Irland). The ejaculator delivers AC voltage in a fashion controlled by the operator, the current being determined by tissue resistance. The probe is equipped with a temperature sensor and a buzzer alerts the operator if the temperature exceeds a set limit (Halsted et al, 1987).

After the patient has been placed on the examination table, the bladder is emptied through sterile catheterisation. When performing sterile catheterisation prior to the procedure, it is important that the lubricant is non-toxic. In our experience glycerol seems to be one suitable alternative. The lubricant that is present on commercially pre-lubricated catheters may be toxic to sperm, and if the patient is on intermittent catheterisation, he should be asked to use glycerol as a lubricant the day prior to the procedure. In order to maintain viability of sperm in the retrograde ejaculate, the urinary bladder is washed before stimulation, and 20-75 ml of fresh HEPES buffered balanced salt solution, supplemented with albumin, is instilled in the bladder.

A digital rectal examination is done, followed by proctoscopy, to make sure that the rectal mucosa is intact.

The probes are available in different sizes and with different arrangements of the electrodes. We have found a probe with three perpendicular electrodes to be the most effective. When introducing the probe into the rectum, the electrodes should be directed anteriorly. After the probe has been positioned correctly, the stimulations starts by increasing the voltage, from 2 volts up to 5 volts, and lowering it again in a wavelike pattern. If no emission occurs, the voltage is increased in increments of 3 volts for each stimulation up to a maximum of 35 volts or until ejaculation occurs. When it is clear that the patient has

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no more fluid coming out of the urethra, the procedure will stop. It is followed by proctoscopy to ensure that no damage has been incurred to the rectal mucosa.

The procedure usually requires three persons in addition to the anesthesiologist. One monitoring the blood pressure and other vital parameters, one performing the EEJ and a collector sitting opposite the person performing the EEJ. It is important that these last two persons have good eye contact during the event. The assistant has to direct the semen into the sterile specimen container and also to milk the bulbous urethra. The milking is important as emission is not accompanied by forceful projectile ejaculation. When no anterograde ejaculation occurs, one can expect a retrograde ejaculation, provided the patient achieved a good erection during the procedure.

After the stimulation, catheterisation of the bladder is done and the bladder is flushed with the same solution as above. If the person is not habitually using intermittent catheterisation he should take oral antibiotics for three days, to avoid the risk of urinary tract infection.

The semen in its various fractions, anterograde and retrograde, is then taken to the laboratory for further analysis and preparation.

3.1.3 Anaesthesia

If the patient has to be treated under general anaesthesia, the anesthesiologist should be aware of the risk of eliciting autonomic dysreflexia (AD) (Rocco, 1959). The anaesthesia is induced with propofol (Diprivan®, Zeneca, Cheshire, UK) 1.5-2mg x kg^{-1} (BW), and in some cases supplemented with alfentanil (Rapifen®; Janssen-Cilag, Beerse, Belgium) 0.5-1 mg. This is done with the patient lying on his back. The anaesthesia is maintained with propofol 0.1-0.2 mg x kg^{-1} x min^{-1}. Ventilation is carried out by assisted mask ventilation, except if the patient is obese or if there are other contraindications for keeping the patient on mask ventilation. After induction of anaesthesia the patient is turned on his side.

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3.1.4 Testicular biopsy

The absence of live sperm in the ejaculate can be explained by either an occlusion of the genital tracts, by necrozoospermia or by hypospermatogenesis. If retrieval of live sperm fails with EEJ, the alternative is to try to retrieve sperm either from the epididymis or from the testis (Watkins et al, 1996). Tissue can be obtained either by open procedures such as Testicular Sperm Extraction (TESE) or by percutaneous aspiration Testicular Sperm Aspiration (TESA) (Craft et al, 1997), the latter presumably less traumatic.

3.1.5 Autonomic dysreflexia

AD is a paroxysmal medical condition in patients with lesions at, or rostral to, the T6 spinal cord segment (Bannister and Mathias, 1992). It is a result of increased vasopressor responses to stimuli below the level of lesion (Head and Riddoch, 1917, Johnson et al, 1975). Both PVS and EEJ can cause severe AD. These patients have no supraspinal control of sympathetic autonomic neural outflow to the large splanchnic circulatory bed and to the heart, something which is of major importance for blood pressure homeostasis. Symptoms include pounding headache, profuse sweating above injury level, goose bumps, pupillary dilatation, nasal congestion, skin blotching and slow pulse. The headache is usually in the occipital or frontal region. AD can also lead to cardiac dysrhythmias (Kurmick, 1956). Below the lesion the patient will get cold peripheries and piloerection.

Several days after the occurrence of AD there is a sustained increased sensitivity to stimuli that can cause this reaction, e. g. a full bladder. The patient is therefore instructed to catheterise the bladder more frequently for some days, and patients emptying the bladder by tapping should use intermittent catheterisation instead during this period. The first time the syndrome of AD occurs for a tetra- or

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paraplegic person it is a scary experience. It is important that medical professionals know about this syndrome to avoid inappropriate treatment. AD has been treated primarily with a calcium ion channel blocker, nifedipine, (Adalat®, Bayer, Gothenburg, Sweden) which has proven very effective (Steinberger et al, 1990). It could be used prophylactically against AD prior to PVS or EEJ, but, since nifedipine has a negative effect on sperm fertilising ability (Hershlag et al, 1995), it is not used extensively in our unit for this purpose.

3.2 Treatment of infertility

3.2.1 Infertility work-up

A proper diagnosis is a prerequisite for effective treatment of infertility (Linsenmeyer and Perkash, 1991). It is crucial, however, that the diagnostic effort is not overdone. It is the responsibility of the physician to decide what the optimum diagnostic intervention encompasses in order to embark onto ART. The infertility work-up starts at the spinal outpatient unit, where the medical history of the couple is recorded and blood samples are retrieved for determination of FSH as well as HIV and hepatitis serology. Orchidometry is also performed at this visit.

3.2.1.1 The female

The female partner in the couple seeking help for infertility is interviewed and undergoes a routine gynaecological examination, including vaginal ultrasound. Further diagnostic measures are considered unnecessary if no suspicion of pathology emerges from the previous steps.

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3.2.1.2 The male

If the patient has a spinal injury rostral to T10, PVS is tried first. The partner may be present during the procedure. The vibrator is applied to the glans penis and stimulation lasts for approximately three minutes. If ejaculation has not occurred after ten such attempts, the procedure is discontinued and the patient will be asked to come back for a second visit.

At the second visit vibratory stimulation is tried again, now in combination with metoclopramid and physostigmin. Because physostigmin causes vegetative symptoms, such as nausea, with ensuing risk of vomiting and aspiration, patients are asked to be fasting.

Finally, if this does not work and GA is not required, EEJ is performed at the outpatient unit. If the patient has residual sensibility in the perineal area, GA is needed for EEJ, and the procedure is carried out at the Department of Obstetrics and Gynaecology at Huddinge University Hospital. If no sperm are retrieved with these techniques, the patients are offered an open testicular biopsy, testicular sperm extraction (TESE) or testicular sperm aspiration (TESA) as a last means of diagnostic intervention.

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3.2.2 Home insemination

If the female is under 30 years of age and if the couple has no history of reproductive problems besides those related to the husband's nerve injury, they are encouraged to try to conceive at home. This is preferable from the point of view of quality of life in that it maintains the integrity of the couple. As mentioned below, 65 SCI men out of our patient stock of 483 men, have managed to father children after an injury that occurred up to three decades previously. Some after infertility counselling and by less sophisticated techniques. Others due to incomplete lesions and preserved procreative capacity.

Detailed information regarding how to conduct a home-insemination is conveyed to the couple. The woman is asked to watch for physiological signs, e. g. *spinnbarkeit* of the cervical mucus, that indicates proximity to ovulation, which is the optimal time for insemination. This could also be assessed by measuring LH in the urine. When ovulation is imminent, the man should produce an ejaculate, using whatever means available. The semen should be collected in a small container not previously washed in a dishwasher, since the detergent for dishwashers usually contain substances toxic to sperm.

The semen is aspirated into a syringe and then introduced into the vagina with the tip in close proximity to the portio, which is easily palpated. Once in place, the syringe is emptied.

Another technique that has proven successful in some cases is a combination of a vibrator and coitus. The vibrator is applied onto the glans penis as described above. The normal physiological pattern is that the penis will get erect about thirty seconds before ejaculation occurs. The vibratory stimulation is done with the man lying on his back. When he feels that ejaculation is imminent, the woman can then mount on top of the man, finishing the excitation by coital stimulation. The man will then ejaculate into her and hopefully conception can occur as during normal coitus. Among our patients, at least three have managed to conceive this way over the last eight years. The true number may be higher.

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3.2.3 In vitro fertilization and intracytoplasmic sperm injection

If the couple has tried home insemination for a year without success, they are offered more advanced forms of ART. The use of IUI in the treatment of male infertility is widely spread. IUI bypasses the cervical mucus barrier and increases the fertility potential by depositing a high density of gametes at the site of fertilization. However, if done in non-stimulated cycles the pregnancy rate in large materials is only 3.1% (Ombelet et al, 1995). In order to obtain a modest increase in success rate for IUI, the female work-up has to be similar as for IVF and ICSI, (Sönksen et al, 1992) which makes the method much more expensive and demanding, without coming near the effectiveness of IVF/ICSI (Table VI). Intra-uterine insemination (IUI) was practised unsuccessfully in a few cases during 1990 at our unit with both PVS and EEJ.

If the semen quality is very poor or if there are female infertility factors present, IVF with or without ICSI is the method of choice. The availability of IVF, and later ICSI, dramatically improved the prospects for men with SCI or TC to become fathers. It was in July 1978 that Louise Brown, the first child concieved with IVF, was born. Since then more than 100 000 children have followed. (Steptoe and Edwards, 1978). IVF should be considered in all cases when other standard treatment techniques have failed, especially in cases of severe male infertility, such as is the case with many TC patients (Ohl et al, 1991).

3.2.3.1 Ovarian stimulation

The patient couple is interviewed and thoroughly informed at the IVF unit before onset of treatment. After securing the absence of contraindications to IVF/ICSI, such as progressive debilitating disease, ovarian

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failure or cognitive problems that may jeopardise compliance with treatment protocols, IVF/ICSI can then be performed in a natural menstrual cycle, but much more effectively in cycles of controlled ovarian hyperstimulation (COH). At Huddinge University Hospital, the standard protocol for COH requires downregulation of the pituitary using analogues of gonadotropin releasing hormone (GnRHa). Preferably, this drug is administred by the nasal route and treatment is commenced either on cycle day 1 or 21 of the menstrual cycle. In the former case, a vaginal ultrasound scan is performed after three to four weeks of medication and an endometrial thickness of 4 mm is considered a sign of ovarian quiescence. If GnRHa treatment is initiated on cycle day 21, the patient is interviewed over the phone about the occurrence of menstrual bleeding and signs of low estrogens after about three weeks of medication. Stimulation with gonadotropins (Gn) starts as soon as ovarian quiescence is established and it is timed so that oocyte pick-up (OPU) could be done in the beginning of the week. The drug is self-administered as subcutaneous injections. In order to evaluate the effect of the Gns, a blood sample is collected and analysed for estradiol on day 6 of stimulation. If the ovarian response is too strong, the dose is reduced, so as to avoid the risk of ovarian hyperstimulation syndrome. If, on the other hand, the response is too weak, the dose may be increased. Provided the ovarian response on day 6 was adequate, the patients come to the IVF unit on day 10-12 for pelvic ultrasound and for determination of serum estradiol. In order to induce final oocyte maturation, human chorionic gonadotropin (hCG) is administered when there are several follicles >18 mm as estimated by ultrasound.

3.2.3.2 Oocyte Pick-Up

OPU is performed 37 hours after the hCG injection. The woman is anaesthetized with alfentanil and midazolam (Dormicum®, Roche, Stockholm, Sweden) and she also receives local anaesthesia of the fornix vaginae. If possible, the husband should be present as a support during the procedure, so the

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OPU/ET room should therefore be wheelchair accessible. The ovaries are accessed by the vaginal route for follicle aspiration, using a vaginal ultrasound probe for guidance. Oocytes recovered from the aspirates are washed in a balanced salt solution supplemented mainly with albumin and HEPES and transferred to culture medium. Since even slightly subphysiological temperatures cause adverse effects in oocytes and embryos (Almeida and Bolton, 1995) it is adamant that all media and containers are pre-warmed and that all work surfaces are heated.

3.2.3.3 Sperm preparation

Assisted ejaculation or testicular biopsy is performed as described above. Recovered sperm are evaluated by computer-assisted semen analysis (CASA) (Cell Soft, Cryo Resources, NY, USA) and sperm count and motility are determined. Frequently, however, the ejaculates contain large amounts of debris and cellular material (Denil et al, 1992; Engh et al, 1993), and CASA may not be feasible. In these cases, a Makler counting chamber can be utilised instead. Depending on the nature of the sample, separation of sperm and seminal plasma is usually accomplished in one of two ways; by self-migration of sperm or by density gradient centrifugation. In the former case, washing medium (see above) is layered on top of semen in test tubes and after incubation at 37° C for 30-60 minutes, part of the top layer, ideally containing only motile sperm, is harvested. The sperm suspension is further washed by centrifugation/dilution steps and, after CASA, finally diluted to the appropriate concentration. If the proportion of motile sperm in the ejaculate is very low, density gradient centrifugation can be used for sperm preparation. Semen is layered on top of a two step density gradient of silane coated colloidal silica particles, (PureSperm, Nidacon AB, Gothenburg, Sweden) in a balanced salt solution and centrifuged. Following washing the sperm suspension is analysed by CASA and finally diluted to the appropriate concentration.

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Biopsy material is finely cut and shredded using scalpels. The tissue is transferred to a conical test tube and allowed to sediment. The pelleted material is distributed among microdroplets under oil in a Petri dish. The dishes are then incubated for several hours before being checked for presence of motile sperm. In cases of severe hypospermatogenesis, the biopsy may be performed one or two days before the OPU in order to let more motile sperm emerge from the structures (Edirisinghe et al 1996). Frozen thawed sperm and testicular biopsy material can successfully be used for ICSI, thereby reducing the need for repeated EEJ procedures or biopsies.

3.2.3.4 Fertilization, culture and embryo transfer

For standard IVF, oocyte-cumulus complexes are distributed among droplets under oil in Petri dishes. Twenty thousand prepared motile sperm are added to each droplet. ICSI was usually performed in cases of low count, i.e. $< 0.5 \cdot 10^6$ motile sperm after preparation, $< 20\%$ motility, $\geq 95\%$ abnormal sperm, or, when previously fertilization failure had occurred. For ICSI, the oocytes are denuded of their investment cells by treatment with hyaluronidase. The denuded oocytes are inspected for presence of the first polar body, indicating nuclear maturity, as well as signs of atresia. Mature oocytes are distributed among droplets under oil arranged around a central droplet containing sperm in a highly viscous solution of polyvinylpyrrolidon (PVP). In an inverted microscope with 200x magnification motile sperm are identified. By the use of a precision-made capillary injection pipette controlled by micromanipulators, the sperm are immobilised, picked up and finally injected into the oocyte.

The day after insemination for standard IVF or ICSI, the presence of two pronuclei, indicating normal fertilization, is recorded. In the case of standard IVF, the eggs are moved to droplets of fresh medium. The eggs are further cultured over night until the day of transfer. On that day, the two embryos that exhibit the

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most regular morphological features are selected for embryo transfer, whereas others of good morphology are cryopreserved (Lasalle et al, 1985). For embryo transfer, the couple comes together to the IVF unit. The woman should have a filled bladder to facilitate visualisation of the uterine cavity by ultrasound and also to straighten the passage through the cervix, allowing a much smoother insertion of the transfer catheter. No medication is given unless there are anatomical or other reasons to expect a painful procedure. A transfer catheter is loaded with the embryos and then passed through the cervix. Afterwards, the woman stays supine for about 15 minutes, during which time the couple receives instructions about the luteal phase support as well as about the pregnancy test.

4. RESULTS

4.1 Semen retrieval and analysis

Semen analyses were requested by 127 men [level of injury C2-L3, ASIA impairment grade A - E (Ditunno et al, 1994), median age 27 (range 17 -53)] and subsequently performed. Azoospermia was seen in 11 men. The results of semen analyses in 45 cases of SCI men, where CASA could be performed, are shown in Table 1. (see also App 2).

Table I. Results of semen analysis in ejaculates obtained by PVS or EEJ in men with acquired SCI. Numbers are median (range). When more than one sperm sample was analysed, the average value was entered.

Number of patients:	45	
Total sperm count $x10^6$	130	(0-978)

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Sperm motility (% motile)	10	(1-88)

The results of the semen retrieval procedures in 66 men of couples seeking infertility counselling are shown in Figure 3. It appears that PVS, with or without physostigmin, was effective in two thirds of the cases, corresponding to the proportion of men with lesions above T10. EEJ was required to obtain semen from the remainder. Live sperm were found in 63/66 cases. Testicular biopsy in the three azoospermic cases showed Sertolicell-only syndrome.

The criteria for evaluating sperm morphology changed during the study period and an analysis of the combined material is not feasible.

Ejaculates achieved through PVS or EEJ, especially the first time after a long period of abstinence, varied considerably both in the SCI and the TC groups. The first ejaculate often had a rusty or brownish colour, which made CASA difficult to perform. In such cases, analysis in a Makler chamber was often performed.

4.2 ART in couples with SCI men

The algorithm for management of the infertile SCI man is shown in Fig 3, page 95**.**

About half of the men that requested semen analysis decided to have infertility counselling with their partners (n=67). During the study period, eleven of the couples were divorced and the male partners have not returned for counselling with another female partner, with one exception. Nine couples have had biological children on their own after counselling. It is difficult to ascertain what techniques were actually used in those cases and to estimate how many cycles were required to achieve these results and, as in all pregnancies, paternity can only be verified by HLA testing, which was not indicated in these cases. Nine

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couples decided to cease efforts to have children without resorting to advanced ART. Among these, two couples had children from before the injury or from previous relationships. Thirty-six couples choose to embark on advanced ART. For a summary of the outcome, see Fig 3, (page 95).

4.3 Paper I and Paper III (IVF and ICSI in men with SCI)

Paper I concerns the feasibility of assisted ejaculation in combination with IVF, which was the most advanced form of ART available at our unit during the initial study period. The aim was to obtain an indication of whether IVF would improve delivery rates over that which could be achieved with insemination. Ten patient couples were treated and success was reached even in cases where only 200 000 sperm could be retrieved after preparation. However, as can be seen from Table II, there were four cases of total fertilization failure. During the second period from May 1994 to June 1996 when ICSI became available, all treatment cycles but one led to embryo transfer. In this cycle only one egg was retrieved, fertilized by ICSI and cryopreserved.

Table II. Clinical results from combining assisted ejaculation and IVF or ICSI in couples with SCI men. ICSI was available from May 1994 onwards.

Study period	No. of cycles	No. of fertilization failures	No. of ETs	Clinical pregnancies
Jan -92 - April -94	26	4	21	9 (35%)
May -94 - Jan -96	27	0	26	7 (26%)

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Paper III is an extension of the study of Paper I , and thus includes all subjects from the latter paper. It concerns the utility of ICSI in this patient group. It appears from Table II that fertilization failure can be avoided with ICSI and that treatment can be offered in cases unsuitable for IVF. The benefit of ICSI is further demonstrated by comparison of sibling oocytes from seven patients that had been fertilized with either IVF or ICSI. Oocytes from three patients failed to become fertilized with IVF, whereas all patients had fertilized oocytes using ICSI (Table III).

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Table III. Results of fertilization with IVF and ICSI

 in sibling oocytes.

Case	Fertilization with IVF		Fertilization with ICSI	
1	1/2		1/3	
2	5/6		6/6	
3	0/7		6/11	
4	2/5		3/12	
5	3/9		6/10	
6	0/4		7/8	
7	0/3		6/7	
Average	11/36	(31%)	35/57	(61%)

Table IV shows the laboratory results from IVF/ICSI in the 53 treatment cycles. For IVF the average fertilization rate was 46% per oocyte when only conventional IVF was available. When ICSI was part of the treatment, fertilization rate for ICSI was 57% and conventional IVF during this period dropped to 33% (Table IV).

Table IV. Laboratory results from 53 treatment cycles combining assisted ejaculation and IVF or ICSI in couples with SCI men. ICSI was available from May 1994 onwards.

Study period	No. of eggs	No. of fertilized eggs	No. of cleared eggs	Mean no. of embryos transferred

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Jan -92 - April -94 (IVF)	289	134	(46%)	116	(87%)	2.3
May -94 - Jan 96 (IVF)	92	30	(33%)	29	(97%)	2.0
May -94 - Jan -96 (ICSI)	182	106	(57%)	94	(89%)	2.1

4.4 Paper II (IVF after TC)

From January 1993 to August 1994, ten couples with long-standing infertility due to anejaculation or retrograde ejaculation after treatment for non-seminomatous germ-cell tumor (NSGCT) that all had undergone RPLND were treated at our unit. All these men underwent diagnostic EEJ under GA. We found spermatozoa in nine cases and the anteROgrade fraction was perpared for use in IVF. In three cases, however, the sperm quality was so impaired that normal IVF was considered impossible. The ten men (median age 34 years, range 28-40) had all undergone unilateral orchidectomy and RPLND 5-14 years (median 10 years) earlier. Eight of them had received chemotherapy. All of these men reported normal sexual arousal, erection and active sexual life but inability to ejaculate during coitus.

Most men with TC in this study had ejaculatory disturbances as a result of nerve injuries after bilateral RPLND. More recent approaches saves the superior hypogastric plexus and the sympathetic nerves controlling ejaculation. If diagnostic RPLND is conducted it is carried out unilaterally. Some men with retrograde ejaculation after RPLND can use alpha-sympathomimetic drugs such as imipramin and efedrin. (Nijman et al, 1982). This can affect the ejaculation and restore the anterograde fraction. Some men in our study tried efedrin without any success.

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Concerns have been raised regarding mutagenic effects in offsprings from matings with spermatozoa obtained from men during or soon after treatment with chemotherapy. Animal studies have shown that chemotherapy will induce a high rate of chromosome anomalies in meiotic and post-meiotic cells (Meistrich, 1993). The relevance of this finding in humans has been discussed. However, there is no evidence of an elevated risk for genetic defects in offsprings of male patients treated with chemotherapy (Babosa et al, 1994). There is a recommendation that spermatozoa are not obtained for this use until six months after the last treatment (Meistrich, 1993).

Emission of semen was achieved by electroejaculation in all ten men included in the study. In four men azoospermia or extremely severe oligozoospermia was seen, most probably caused by chemotherapy. The clinical results from the combined use of IVF and EEJ in our study are summarised in Table V. A very high implantation rate, 86%, was observed in this study. For details regarding laboratory data, see Paper II.

Table V. Clinical results from IVF using semen obtained by EEJ from six men with anejaculation after RPLND.

Number of IVF cycles	6
Number of fertilization failures	1
Number of embryo transfers	6*
Number of pregnancies	6**
Number of deliveries	5

* Including one from cryopreserved embryos.

** Of which five were twins.

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4.5 Paper IV (Semen in men with myelomeningocele)

As advanced ART develops further, it opens up reasonable prospects for men that earlier were thought of as infertile, such as many MMC men, to father children. Our center serves as an outpatient unit for all SCI patients in the greater Stockholm area, including a large number of young adults suffering from MMC.

During our annual examinations of MMC patients, it became obvious that there was a demand to explore the fertility and to provide these men with information about their procreational status. A protocol was designed where men expressing an explicit desire to have their fertility potential examined were enrolled. Nineteen of 46 men evaluated at the annual examination showed an initial interest. Nine of these 19 men were subsequently included in the study due to their explicit desire to go through an EEJ and possible testicular biopsy.

The level of lesion ranged from T12 to L4 and ASIA Grade from A-D (see Table I in Paper IV).

Out of the nine men, two could produce an unassisted ejaculate, (one through traditional manual masturbation and one by putting the foot in a bucket of ice-water). The remaining seven needed assisted ejaculation, and produced anterograde and retrograde ejaculates after EEJ in GA. In one of the unassisted ejaculations, sperm could be retrieved. Out of the seven EEJ, four patients had sperm in their ejaculates. Testicular biopsies were performed in seven patients as shown in Table II in Paper IV.

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Seven of the nine men had FSH levels above the upper limit of the normal range and testosterone was in the lower normal range. The testicular volumes did not exceed 15 ml. There was no correlation between the level or completeness of lesion and semen quality, testicular size and hormone levels.

This pilot study showed that MMC men that can not procreate by themselves have a reasonable prospect of becoming fathers through modern ART. Since MMC patients show less compliance with health care providers (Malone et al, 1994), it is important that the aspect of fertility is brought forward in a proper context during their habilitation. It should be the responsibility of a modern rehabilitation facility to address the issue of adolescence in a proper and correct way. Several studies indicate that young men and women with MMC have a self-perception that corresponds very closely to normal. Against this background diagnostic interventions may very well be justified.

4.6 Paper V (Anaesthetic management of electro-ejaculation)

AD is a syndrome that occurs in 85% of SCI patients with lesions at or rostral to T6. It is caused by noxious stimulations below the level of injury and involves severe arterial hypertension, headache, sweating above the level of injury, pilo-erection, mydriasis, nasal congestion and bradycardia (Johnson et al, 1975). Many medical professionals not acqainted with SCI care are not aware of this syndrome and the potentially severe complications that can follow.

It was considered important to implement a protocol that would ensure optimal conditions for semen retrieval under EEJ and PVS while not exposing the patients to an unjustifiable risk.

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During the time from January 1991 to September 1997, 87 EEJ procedures in GA were performed at our unit. This included 30 SCI patients and 15 patients treated for TC in the form of non-seminomatous germ cells tumors (NSGCT) that had undergone RPLND and therefore needed EEJ in order to ejaculate. Seven SCI patients had a neurological level at or rostral to T6, and thus at risk of AD.

Twenty-two EEJ procedures in GA were performed on these seven patients and out of these 22 procedures, six episodes with more pronounced systolic blood pressure elevations occurred in five of the subjects. They were treated with calcium ion channel blockers with adequate results. The question was whether alphentanil and propofol could be administred in sufficient quantities in order to avoid the pronounced systolic blood pressure elevations. In 16 of the 22 anaesthesias performed, the systolic blood pressure never exceeded 160 mmHg, even though the EEJ stimulation went up to 30 volts during two occasions.

No adverse events occurred in the SCI group. In the RPLND group, one case of aspiration lead to a mild pneumonia that required hospitalisation overnight. One other patient had a brief episode of post-operative confusion.

5. DISCUSSION

5.1 Semen retrieval and assisted reproduction after SCI

Trials of unassisted ejaculation is always warranted in both SCI and RPLND/TC men prior to embarking on assisted ejaculation techniques. The reported success rate with PVS in SCI men varies from 32% to 96%, depending on the level and completeness of the injury (Sönksen et al, 1994). If the SCI is rostral to

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T10 it is the simplest way to retrieve semen, if necessary in combination with physostigmin. As AD is a physiological response to PVS in 85% of SCI men if the lesion is rostral to or at T6 (Alderson and Frost, 1990), the procedure should be performed in an environment were AD can be dealt with professionally. If PVS is performed for procreational purposes and there is a medical history of retrograde ejaculation, the bladder should be washed with a HEPES buffered balanced salt solution supplemented with albumin prior to stimulation, and the bladder catheterized after stimulation for retrieval of a possible retrograde ejaculate.

If the patient is unable to ejaculate with PVS in combination with physostigmin, he is then offered EEJ, to be undertaken in GA if there is residual perineal sensation. This is sometimes difficult to determine prior to EEJ, and the procedure may have to be aborted if the patient reports pain during stimulation. As reported earlier, we have had 100% success in obtaining semen by EEJ even if all ejaculates did not contain live sperm. This is in agreement with reports from other centres (Brackett et al, 1996A).

Electrical stimulation for obtaining ejaculation has been dealt with in more sophisticated and invasive ways by Brindley (1989) and Creasey (personal communication). They have both worked with different versions of a sacral anterior root stimulator. The S2, S3 and S4 roots are connected with a small electric generator to a radio receiver that is placed subcutaneously. With a small radio transmitter the patient can activate the generator and induce micturition, defecation, erection and ejaculation, when operating optimally (Brindley, 1990). When this type of equipment becomes more reliable it may serve as an alternative for the future.

Several studies on semen quality in SCI men have been performed (Brackett et al, 1994A, Ohl et al, 1997, Sönksen et al, 1996, Mallidis et al, 1994, Hirsch et al, 1992, Denil et al, 1992, Siösteen et al, 1990,

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Linsenmeyer and Perkash, 1991). One may conclude that semen profiles differ little regardless of extent and level of injury, except for injuries at T10-T12, that seem to be associated with azoospermia (Chapelle et al, 1993). SCI males that have suffered a large number of urinary tract infections have a lower quality of semen (Ohl et al, 1992; Rutowski et al, 1995). These patients should take antibiotics two weeks prior to semen retrieval for ART. If they are emptying their urinary bladders through clean intermittent catheterisation, they should be asked to use a sterile uncoated PVC catheter with a non-toxic lubricant 24 hours prior to semen retrieval.

External factors such as clothing giving rise to scrotal hyperthermia, frequency of ejaculation, bladder management et cetera seem to have little effect on sperm quality (Brackett et al, 1994B and 1996A). The sperm in ejaculates obtained by PVS are of better quality (Sönksen et al,1996; Brackett et al, 1996A). Brackett recently reported that seminal plasma of SCI men inhibit sperm motility from normal men (Brackett et al, 1996B). This adds a new interesting perspective, where sperm aspirated from epididymis or from vas deferens of SCI men, that have not been in contact with the seminal plasma, could be of better quality and perhaps more suitable for ART.

The hormone levels of the HPG axis is sometimes affected, but to an extent that usually correlate poorly with semen quality (Brackett et al, 1994A).

The effect of repeated EEJ on semen quality has been studied by Beretta et al (1989), Brackett et al (1996A), Engh et al (1993), and Siösten et al (1990). It appears that some improvement in sperm count and motility can be seen, but the clinical significance of these findings is as yet onknown.

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Semen can be obtained by EEJ from most men in the acute stage (Mallidis, 1994). The obvious psychological trauma of adding EEJ to all other procedures and operations in the acute stage demands, according to our opinion, a clear justification by proven benefits to the patient, i.e. it must be shown that chances for fatherhoood are significantly superior by that approach as opposed to performing sperm retrieval at a later stage. Available evidence is conflicting: Brackett (1996A) has reported that semen retrieved in the acute stage sometimes lacks sperm, something which is rarely the case in the chronic stage. By contrast, Mallidis (1994) reported the regular finding of live sperm in ejaculates obtained early after injury.

Testicular biopsy is done to characterise spermatogenesis or to identify mature sperm available for ART. When the technique was first used in our unit, Testicular Sperm Extraction (TESE) was applied, but gradually it has been replaced by Testicular Sperm Aspiration (TESA), (Rosenlund, 1998). Aspiration is done with a butterfly needle. The physician inserts the needle percutaneously into the testicular parenchyma, and the assistant aspirates tissue into the tubing, using a 20 ml syringe. This method seems as effective as open biopsy for retrieval of testicular sperm for ICSI (Craft et al, 1997; Rosenlund et al, 1998). It also seems less traumatic to the patient and particularly to the testes (Harrington et al, 1996). By testicular biopsy, sperm and fertilization can be obtained even in cases of very severe hypospermatogenesis as in non-mosaic Klinefelter's syndrome (Tournaye et al, 1996) and in cases where only spermatids are available (Fishel et al, 1995; Tesarik et al, 1995).

5.2 Practical considerations in treating infertility in SCI men

The goal of the Spinalis infertility services is to help infertile couples to become parents. Against this background, effectiveness of infertility treatment is a prime concern that obviously has to be balanced by consideration of risks, invasiveness and cost. Depending on the level of SCI and the ASIA impairment

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grade, home insemination may be tried as a first step. A number of authors have reported various degrees of effectiveness of home insemination in couples with SCI (Chapelle, 1983; Dahlberg et al, 1995; Hirsch and Lipschultz, 1987; Löchner-Ernst et al, 1997). The results are difficult to interpret since, frequently, information is lacking or incomplete regarding neurological characteristics. It is also difficult to extract information regarding for how long these couples tried and in how many cycles. However, we still believe that, when possible, there are advantages in trying at home first. There are minimal risks involved and a much higher degree of integrity. Out of the over 600 men that have visited the Spinalis unit, 65 have fathered a child after sustaining a SCI. A significant proportion of these SCI men (45/65), complete or incomplete, have reached fatherhood without the assistance of modern ART. These men represent a large variety of lesion levels and degrees of completeness.

In our material, nine couples managed to have a child with home insemination after seeking fertility counselling at our unit during the period from 1990 to September 1997 (Figure 3). Modern ART including IVF and ICSI under GA should of course only be provided when needed.

In our treatment algorithm, IUI is not included (Fig 3). Data compiled by Sönksen and Biering-Sörensen (1992) indicate that the cumulative rate of live born children after combining PVS and IUI was 8% in studies involving 619 men. The combination of EEJ and IUI gave a cumulative rate of live born children of 3% (Table VI). More recent data are presented in Table VI, and it appears that in SCI men, a delivery rate per insemination cycle of about 6% can be expected, which is in agreement with a compilation of reports of 3308 IUI cycles resulting in 259 deliveries (Ombelet et al, 1995). Clearly, IUI is more effective if combined with hormonal stimulation of the woman. This obviously places a physical and psychological strain on the woman and limits the number of treatment cycles that the couple can endure. Furthermore, if the ejaculation procedure involves GA and risks of AD, this adds to the stress on the couple. Last, but not

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least , introduction of a step of IUI before IVF/ICSI will delay effective treatment for a proportion of the patient couples.

Table VI. Reports of treatment of anejaculatory infertility due to SCI by assisted ejaculation and insemination

Reference		No of patients	No of cycles	No of pregnancies	No of deliveries
Thomas et al	(1975)	1	3	1	0
Francois et al	(1978)	1	7	1	1
Bennet et al	(1987 and 1988)	10	42	4	1
Rawicki and Lording	(1988)	1	2	2	0
Ayers et al	(1988)	1	4	0	0
Hirsch et al	(1990)	1	1	1	1
Lucas et al	(1991)	5	8	1	1
Toledo et al	(1992)	10	18	1	1
Buch & Zorn	(1993)	6	21	3	2
Brackett et al	(1995)	22	60	6	6
Blank et al	(1996)	15	31	6	0
Chung et al	(1996)	10	50	5	3
Yamamoto et al	(1997)	12	80	2	2
Sum		95	327	33	18

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Against this background, we feel that it is in the best interest of the patients to move on to the most effective treatment without delay. Thus, IVF or ICSI is performed if home insemination fails. The results from all IVF treatments at our unit involving SCI men between 1992 and September 1997 are summarised in Table VII. Thus, with a delivery rate of 24% per ET, IVF seems to be an effective treatment.

Table VII. Clinical data of IVF treatment in our unit, with or without ICSI, of 36 couples with an SCI male. The pathological pregnancies include one

case of intrauterine death in the 30th week of pregnancy.

Number of couples	36
Number of started cycles	75
Number of OPUs	68
Number of ETs	63
Number of FER	7
Number of pregnancies	20
Number of pathological pregnancies	5
Number of deliveries	15
Number of children	18

Table VIII is a compilation of results of IVF/ICSI/GIFT/Zygote Intra Fallopian Transfer (ZIFT) in SCI men. Although the numbers are small they suggest a delivery rate per cycle of 24%. Possibly, there is a publication bias towards successful cases, so the figure might be an overestimate of the actual delivery rates that could be expected.

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Table VIII. Reports of treatment of anejaculatory infertility due to SCI by assisted ejaculation on IVF/ICSI/GIFT/ZIFT.

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Reference		No of patients	No of cycles	No of pregnancies	No of deliveries
Ayers et al	(1988)	1	4	0	0
Blank et al	(1990)	1	1	1	1
Leeton et al	(1991)	1	1	1	1
Hill et al	(1991)	1	1	1	1
Toledo et al	(1992)	10	15	9	5
Buch and Zorn	(1993)	2	2	0	0
Dahlberg et al	(1995)	9	14	4	4
Bracket et al	(1995)	7	10	5	1
Chung et al	(1996)	1	1	1	1
Yamamoto et al	(1997)	3	7	2	1
Present study	(1997)	36	68	20	15
Sum		72	124	44	30

At the IVF unit of the Huddinge University Hospital the delivery rate per started IVF/ICSI cycle has been fluctuating between 21 and 34% over the last six years. During this period, the results from IVF/ICSI in SCI men has been 20% deliveries per started cycle.

5.3 Assisted reproduction after testicular cancer (TC)

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Fertility after treatment of TC is dependent on whether extensive radiation or chemotherapy has been given and whether RPLND has been performed, the latter commonly leading to ejaculatory dysfunction. The literature suggests that about half of the men that try to become fathers after such treatment succeed (Pont and Albrect, 1997). The availability of effective treatment for infertility due to anejaculation may increase this proportion.

Since the publication of Paper II, an additional seven couples with anejaculation/retrograde ejaculation after RPLND for TC have undergone IVF/ICSI treatment at Huddinge University Hospital, increasing the total to 17. The results of the treatment of these cases have recently been published (Rosenlund 1998). Of the 17 men, two had complete spermatogenic failure. Three occasionally managed to produce a sample by masturbation, whereas the remaining 12 had to undergo EEJ in GA. The sperm count and motility are shown in Table IX.

Table IX. Results of semen analysis in ejaculates obtained by EEJ in anejaculatory men that had undergone RPLND for TC. Numbers are median (range). When more than one sperm sample was analysed, the mean value was entered.

Number of patients	15	
Total sperm count $x10^6$	439	(0-1336)
Sperm motility (% motile)	13	(1-30)

Also in this group sperm counts are high and motility low. The 15 couples in which the men had retrievable sperm underwent 21 treatment cycles using sperm from EEJ (17), masturbation (3) and TESA (1). After 18 embryo transfers, 12 clinical pregnancies were established, of which one was lost in the first

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trimester by spontaneous abortion. The remaining 11 are delivered or ongoing. In addition, frozen embryos were transfered in three cycles, leading to one pregnancy.

Table X is a compilation of reports of treatment of anejaculatory infertility after TC treated by IVF/ICSI, and, for comparison, figures for insemination are included (Ohl et al, 1991). Again, a larger number of treatment cycles are needed to achieve success using insemination, as compared to IVF.

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Table X. Report of treatment by IVF/ICSI of anejaculatory infertility due to RPLND for testicular cancer. The study of Ohl et al using IUI is included for comparison.

Reference		No of patients	No of cycles	No of pregnancies	No of deliveries
Rowland *et al*	(1985)	1	2	1	1
Khalifa *et al*	(1992)	3	3	0	0
Levron *et al*	(1993)	1	1	1	1
Hultling *et al*	(1995)	6	7	6	5
Novero *et al*	(1996)	2	3	1	1
Chen *et al*	(1996)	1	1	1	1
Rosenlund *et al**	(1998)	15	21	12	11
Sum		23	31	16	15
Ohl et al	*(1991)*	*19*	*74*	*7*	*5*

*includes the six patients in Hultling *et al* 1995.

5.4 Semen quality in men with myelomeningocele

The MMC group represents a particular challenge with their common reluctance or inability to maintain contact with health care institutions (Trollman et al, 1996). This is reflected in their often poor somatic status, with contractures and decubitus ulcers more commonly seen than in the group with acquired SCI.

The semen quality of MMC men was much lower than that of the men with acquired SCI. Also, there was a higher incidence of elevated FSH and of atrophic testicles. Atrophic testicles can also be seen in

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acquired SCI provided the injury occurred early in life. At our unit we have seen one tetraplegic patient for sperm retrieval and analysis, injured at C6-C7, who acquired his injury at delivery. The results of the semen analysis and hormone levels are similar to those seen in the MMC group, suggesting that an intact innervation is necessary for normal gonadal development. Poor semen quality can also be seen in men with injuries at the T10-L2 level (Chapelle, 1993).

5.5 General anaesthesia in SCI men

EEJ is performed under GA in patients with spared sensation in the perineal area. Also, EEJ may be performed under GA to reduce the risk of AD (Lambert et al, 1982). Surgical interventions in the lower abdominal and perineal area, such as cystoscopies, have been performed under spinal anaesthesia (Amzallag, 1993). This has not been done for EEJ, since the blockade might impair the ejaculatory response, and may also make the patient hypovolemic by pooling blood in the lower extremities. Occasionally we have performed EEJ under GA in patients lacking anal sensation, but experiencing AD during PVS and specifically requesting to sleep through the next semen retrieval attempt.

During assisted ejaculation, both with PVS and EEJ, AD may appear in mild forms, such as reflex bradycardia, or in more severe forms, such as significant hypertension creating debilitating headache. Besides the death reported by Guttmann (1976), grave consequences of AD in assisted ejaculation have not been reported. Although AD has been described as a life-threatening complication (Alderson and Frost, 1990), it seems that the risk of serious adverse events requiring medication during surgical procedures in SCI men is moderate (Paper V and Lambert et al, 1982). Apart from AD, there are only scarce reports of adverse events after EEJ (Ohl, 1993).

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5.6 Rehabilitative aspects of ART

Classic medicine is focused on diagnosis and treatment aimed at the underlying pathological process. Thus, the traditional biomedical model directs treatment to the cause of disease, with little or no emphasis on the secondary effects of illness. In contrast, rehabilitation medicine takes a more holistic approach (the "biopsychosocial model"), and furthermore emphasises the consequences of disease in terms of impairment (i.e. loss or abnormality of psychological, physiological, or anatomic structure or function), disability (i.e. restriction or lack of ability to perform a task or activity within the range considered normal) and handicap (i.e. the disadvantage stemming from impairments and/or disabilities, in performing a role otherwise normal).

When applying this rehabilitation paradigm to SCI, it becomes obvious that issues related to sexual dysfunction and infertility deserve priority. According to this author, the following propositions corroborate this claim:

1. Traumatic SCI typically afflicts young males.

2. SCI almost always leads to severe impairment of male sexual function.

3. Sexual activity - including intercourse and procreation - is an important part of life for most persons, and especially so for younger persons.

4. Sexual issues are usually neglected in the acute care or general medical setting.

5. Effective treatment is available.

Ethical questions are inevitable when discussing ART. In particular, the following questions have been raised in this context:

1. Does SCI make you less good a parent?

2. Does treatment of infertility in persons with SCI necessitate a stricter practise than otherwise in terms of exclusion criteria and/or outcome assessment?

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Ethical issues are never completely unequivocal and furthermore do not lend themselves to be "solved" by a positivistic scientific approach. Rather, we have to rely on empirical knowledge and hermeneutics.

Studies addressing parenthood after SCI are scarce. A recently performed study in our center (Westgren and Levi, 1994) concluded that SCI does not seem to impair the ability to be a good parent. As to question number two, it may be argued that stricter practises directed at persons with SCI, in the absence of data implying that such persons presumably are inferior parents than the general population, would by definition reflect prejudice and discrimination towards the disabled.

Obviously, the situation gets more complex if the underlying condition leads to impairment of higher cerebral functions, which is sometimes the case in persons with MMC.

Medical inclusion and exclusion criteria exist in order to avoid harm to the man and woman as well as the child *(Primum est non nocere!)*. Also, the Swedish legislation requires that infertility treatment is provided only if circumstances allow the child to be born into and grow up in a complete family. Progressive diseases, such as cancer and multiple sclerosis, can therefore be considered medical contraindications. If the couple suffers from any major psychological problem, substance abuse, psychiatric disorder or severe cognitive dysfunction, these problems would have to be addressed effectively before entering treatment. The final decision is made by the physician in collaboration with the couple, based on personal experience and judgement.

Should we apply psycho-social contraindications? This matter cannot be adequately dealt with through simplistic rules of thumb. There has to be subjective decisions taken by responsible people involved and

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an open discussion can lead to guidelines. If the couple is refused treatment, they may appeal to the National Board of Health and Welfare. This is illustrated by a case in which we were approached by a couple in which the man had MMC and the woman was severely disabled by cerebral palsy. The man underwent electroejaculation and his semen contained enough viable sperm for IVF/ICSI. At the time of the semen retrieval, the couple together were eligible for 160 hours of community attendant care per week. The woman had a severe motor disability and a grave speech impairment, but no known cognitive impairment. The staff felt that this couple should not be treated, and questioned whether it would be justifyable to"create" a child that would be brought up with limited possibilities to interact directly with the parents. The Ethics Committe of the Swedish Society of Medicine was approached, abd found no contraindications to treating this couple. However, the municipal health authority may see the problem from a different perspective. The issue is still pending and the couple has not been in contact with us again.

The discussion has been brought forward whether the couples seeking infertility treatment should be subjected to the same type of investigation as couples that want to adopt a child. A task group within the Swedish Association of Obstetrics and Gynaecology has suggested that no such investigation should be required for ART.

Problems related to sexuality and infertility are important for patients during an early stage after the SCI or surgery for TC (Silber, 1996; Trieschmann, 1992). These persons are often of parenting age, and many seek information about how they can achieve fatherhood despite their newly acquired impairment. However, discussion of these matters is difficult during the chaotic initial phase. The couple is welcome for infertility counselling one year after the injury. This is provided by a small consistent group of people

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that the couple can rely on throughout the counselling period. Knowledge about the fact that most of these men can experience biological fatherhood is crucial in the rehabilitation process.

Even if orgasm as such cannot be achieved with PVS, most SCI men experience positive feelings with the ejaculatory event when seeing the semen being ejected by rhythmic contractions from the meatus.
In our unit, we have a microscope in the PVS room allows the semen to be analysed immediately and the patient can get direct confirmation of the fact that he has motile sperm. Men that have not ejaculated since the occurrence of SCI experience an exuberant happiness and profound satisfaction when they realise that they can produce live sperm. This procedure has an important positive psychological impact on the rehabilitative process.

In Sweden, the number of SCI men with a need for fertility counselling might not support more than two separate treating units for infertility problems. It has been our main goal to adjust the services to the patient's needs and to provide accurate information about the diagnostic and therapeutic resources that are available. By experience it seems that couples seeking infertility counselling frequently have received incomplete information and ineffective care before. Infertility services should be an integrated part of the total rehabilitation management. Thereby it is possible to ascertain that the diagnostic and treatment procedures are goal-oriented and effective.

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5.7 Obstetric and pediatric aspects on ART

A total of 18 children, out of which six are twins, have been born after IVF or ICSI treatment in our center to 15 men with SCI. The mean birth weight was 3110 gram (range: 1250 - 4220). All but one set of twins were born within two weeks of term. One set of twins were delivered in the 30th week of pregnancy and required six weeks intensive neonatal care. In one of these twins the prematurity led to visual impairment that could be corrected with glasses. Two children of the singletons were born with a ventricular septum defect, that had closed spontaneously at the 18 month check up. One child was born with a partial submucosal cleft, that was surgically treated at three month of age. No other malformations have been found. The post natal medical records from all 18 children in the IVF/ICSI group reveal no other discrepancy between this group and the general population. None of the children from the TC group showed any malformations.

There has been theoretical concerns regarding the safety of ICSI. Questions have been raised regarding effects of mechanical and biochemical damage to the oocyte and introduction of foreign materials such as viruses, bacteria or part of the oocyte membrane. This could imply a risk factor for the embryo. Wennerholm (1998) reported on 840 children born after ICSI, and major malformations occurred in 24 (2.9%) of the infants. Bonduelle (1998) showed in a follow-up study that 46 (2.3%) children out of 1987 needed some kind of surgical correction. This indicates no significant increase in malformations after ICSI, as compared to children born without ART.

Multiple pregnancy is a common complication after assisted conception. It involves a significantly increased morbidity in both mother and child. Thus, anemia, hypertension and gestational diabetes are more common, as is preterm birth with sequelae. Furthermore, the family situation after multiple births is

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very demanding, even if the children are healthy. In families with a disabled parent, multiple pregnancy could strain the resources even more. Thus, there are compelling reasons to reduce the frequency of multiple pregnancy after ART (Nygren and Wikland, 1997). In IVF/ICSI, this could be achieved by reducing the number of embryos transferred. The risk of a lowered pregnancy rate in the treatment cycle could be at least partly offset by an increased number of replacement of frozen/thawed embryos. This may particularly be considered among couples with anejaculatory infertility after TC that seem to achieve a very high implantation rate (Paper II).

All of the 15 SCI couples that have become parents through IVF or ICSI at our center are still living together. The majority of these families receive welfare allowances, and this in turn makes their financial situation better than that of the average family. Thereby, there are improved opportunities for the partners to share parenthood and support each other. Most of these men have been coping very well with their new situation as fathers, and the children develop an understanding of what they can do together with their father in wheelchair and what they can do with their ablebodied mother (personal experience).

The child born into a family that has experienced an interval of infertility is in most cases extra welcome. In the SCI families the expectations of ever getting biological children have in general been very low. As a result of the low expectations the children born into these families have been thought of as miracles and are even more welcome.

6. CONCLUSIONS

- Using assisted ejaculation and IVF/ICSI, a cumulative delivery rate of around 50% can be expected in couples in which home insemination has been unsuccessful. ICSI allows treatment also in cases of

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- extremely severe oligozoospermia or when only testicular sperm is available. Since IVF is more effective than IUI and the latter is ineffective unless performed in combination with hormonal stimulation of the woman, making it nearly as much invasive, IVF/ICSI is the method of choice if home insemination fails. IVF is strongly indicated if EEJ in GA is required, the semen quality is poor or if there are concurrent female infertility factors.
- A high cumulative pregnancy rate can be expected from EEJ and IVF/ICSI in men that are anejaculatory after TC/RPLND. Since semen retrieval in most instances requires EEJ in GA, IVF/ICSI should be employed.
- A sizeable proportion of men with MMC seems to have enough sperm for ICSI, retrievable by EEJ or TESE.
- The risk of severe hypertension and other complications from EEJ of SCI men in GA with assisted mask ventilation in a day surgery setting seems small, provided anaesthesia is managed by experienced staff.

Research in the SCI field throughout the last decades has focused on topics mostly of theoretical interest. In the light of the extended life span of this group of patients, there is a need for a paradigm shift in the direction of patient-oriented applied research, based on the functional analyses of the physically impaired.

People with disability have the same demand as everybody else on society for information, community services, and health services. However, reproductive issues encountered by people with physical disabilities are different from those encountered by people without disabilities. Congenital disability is likely to affect sexual development to a larger extent than acquired disability (Trollman et al, 1996). Disability affects fertility as well as sexuality. Intimacy and spontaneity are more difficult to achieve, and, therefore, counselling of these men and women becomes important. It is necessary that the staff is

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knowledgable of all aspects of the infertility and sexology and that they can assist the patient soon after injury. This brings in a political aspect of the entire rehabilitation process after an injury that causes infertility. The disabled person has the right to information regarding reproduction that is comprehensive and accurate. Preconceived notions on the part of caregivers judging such couples less suitable as parents does not justify withholding information. As modern medical technology provides more options to treat infertility, it is the responsibility of society to make these services available for this category of patients.

A significant hurdle in the pursuit of parenthood for couples with an SCI man is the lack of information and inadequacy of support regarding sexuality and fertility. Hence, information about the good prognosis for achieving pregnancy, and the excellent ability of these families to cope, must be disseminated to the primary caregivers.

It is important to stress that the primary objective of our infertility service is to help childless disabled persons to become parents. We have focused on the clinical outcome rather than on extensive diagnostics. The development of effective techniques for enabling people with physical disabilities to become parents serves as a powerful affirmation of the commitment of the rehabilitation team. This, in turn, leads to empowerment of the disabled individuals.

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Fig 3. Algorithm for infertility treatment of couples with SCI
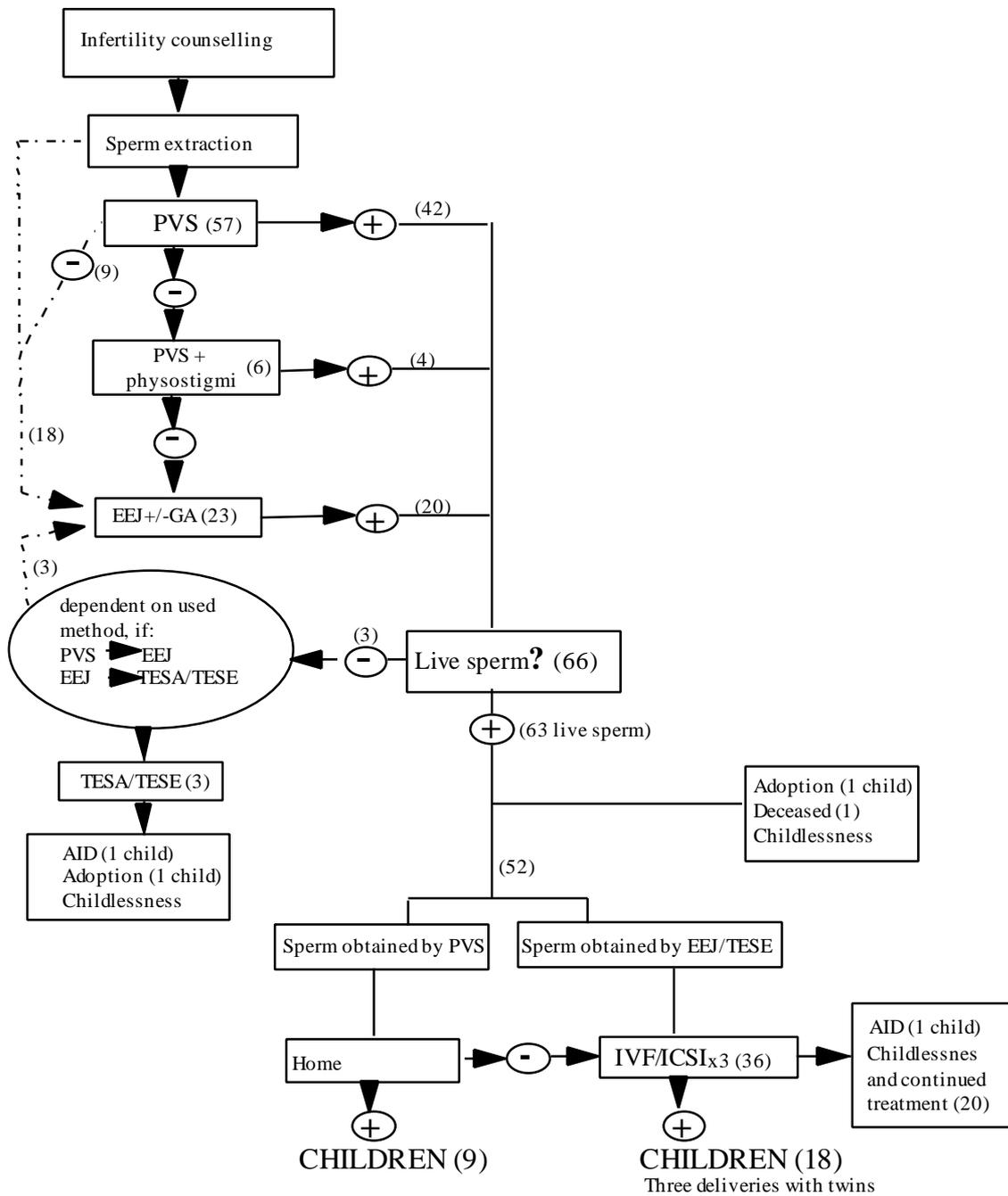
Infertility counselling

Sperm extraction

PVS (57) → + (42)

− (9)

− PVS + physostigmi (6) → + (4)

(18) −

EEJ+/-GA (23) → + (20)

(3)

dependent on used method, if:
PVS → EEJ
EEJ → TESA/TESE

(3) − Live sperm? (66)

+ (63 live sperm)

TESA/TESE (3)

AID (1 child)
Adoption (1 child)
Childlessness

Adoption (1 child)
Deceased (1)
Childlessness

(52)

Sperm obtained by PVS

Sperm obtained by EEJ/TESE

Home → − → IVF/ICSI$_{x3}$ (36) → AID (1 child) Childlessnes and continued treatment (20)

+ CHILDREN (9)

+ CHILDREN (18)
Three deliveries with twins

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This figure describes the actual treatment protocol of patients in this study. Number of patients are indicated in brackets, as well as outcomes. Note that the algorithm is not to be seen as a recommendation of the optimal treatment protocol, but merely to summarises the protocol used in this study (January 1991- September 1997). See discussion for further comments.

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SOME BACKGROUND ON NORMAL PHYSIOLOGY
Normally, each month a follicle develops in the ovary and bursts about 14 days after menstruation. This is called ovulation and is a process that some women feel. The follicle is then usually 20 to 26 mm in size but the egg it contains is only 0.1 mm in size. Growth of the follicle is controlled by the pituitary gland through the hormone FSH (Follicle Stimulating Hormone). The signal that *ovulation* should occur also comes from the pituitary in the form of a rapid release of the hormone LH (Luteinising Hormone, ovulating hormone). Normally, the egg is released from the follicle into the oviduct. With the help of fine, hair-like cilia, the egg is transported to the uterus. *Fertilisation* occurs in the *oviduct* to which sperm have swum via the uterus. After fertilisation, the egg divides and is known as an *embryo*. The embryo grows and becomes fixed in the *uterus* about one week after ovulation if a pregnancy occurs.

IN VITRO FERTILISATION (IVF)
If the oviducts are damaged or missing, the IVF method can be used. The expression means "fertilisation in glass" although the expression "test tube fertilisation" is often used. The principle of IVF is that *eggs are removed from the ovaries and are combined with the man's sperm* to allow fertilisation. If fertilisation and division of the egg occur, the egg is returned to the uterus so that it can grow and result in a pregnancy. The process is carried out as follows.

HORMONE STIMULATION
In principle, one should be able to remove one single egg that develops normally each month and use it for IVF. This was what was done in 1978 when the first IVF baby was born. However, if only one egg is used, the chances of a pregnancy are very small. Through hormone stimulation, one can produce *many eggs and increase the chances* significantly. In the most common form of hormone stimulation, one first *blocks* the woman's own hormone production using a nasal spray (Suprecur or Suprefact) for 2-4 weeks. After checking that the hormones are blocked ("down-regulation"), *hormone stimulation* is begun with injections containing FSH (Gonal For Puregon). Since this causes a strong stimulation of the ovaries, one must therefore monitor the process very carefully to avoid overstimulation. Monitoring is carried out by analysing oestrogen levels (the female sex hormone) in blood samples and by using *ultrasound examinations*. When the hormone stimulation draws to an end, a number of follicles have usually developed in both the ovaries with sizes of more than 18 mm. Then an injection of Profasi ("evening injection") is given to signal that ovulation should occur in the same way as when LH is released normally. This injection starts a biological clock and ovulation begins after 39-40 hours. This is why the *eggs are retrieved after 36-37 hours.*

EGG RETRIEVAL
Egg retrieval is performed using ultrasound-guided puncture of the ovaries. The ultrasound probe is inserted into the vagina and the follicles in the ovaries can be seen on a TV screen. Following *local anaesthesia* of the vaginal wall, a thin needle can be pushed from the vagina into the ovaries to suck out follicle fluid that contains the egg. In the laboratory, this fluid is investigated under a microscope and the egg is isolated. On average, 5-10 eggs are obtained.

SPERM SAMPLES
On the same day as the egg removal, the man provides a *sperm sample*. This must be further processed to be used for IVF. Normally, sperm swim up from the vagina, through the uterus and into the oviducts

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where fertilisation occurs. During this process, the sperm become separated from the seminal fluid. This is important since seminal fluid has been shown to stop fertilisation of the egg. Therefore, one must carry out this separation in the laboratory. This is performed using a method called "swim up". A nutrient solution is carefully layered over the sperm sample in a test tube. After a while, some of the sperm have swum up into the solution and can be used for IVF. The seminal fluid remains in the test tube.

FERTILISATION AND CULTURING
About 20 000 sperm are added to each egg. One of these will fertilise the egg in the same way as normally occurs in the oviduct. The *number of fertilised eggs varies* from one treatment to the next, depending on the degree of maturity of the egg and the quality of the sperm sample. On average, 60-80% of the eggs are fertilised. This is why it is suitable to retrieve more than four eggs.

The eggs and sperm are stored in an incubator that produces a similar environment to that in the oviduct. The salinity, acidity, temperature, humidity and carbon dioxide level are carefully regulated. The eggs and sperm remain in a solution that contains nutrient substances including sugar. Antibiotics are also added to reduce the risk of bacterial growth in the nutrient solution. All this work is carried out aseptically.

Eggs and sperm are cultured for two to three days in the incubator. After the *first day, the eggs are examined under a microscope for signs of fertilisation*. At the same time, the nutrient solution is changed. After the *second day, a check is made to see if division has occurred*. If the culturing has been successful, the egg will have divided and usually contains between 2 and 4 cells on the second day. The eggs are now called embryos (or pre-embryos).

EMBRYO TRANSFER
Then it is time to return the treated and divided eggs to the uterus (a process called embryo transfer). From the patient's point of view, this is a *simple procedure* that can be compared to a gynaecological examination. The embryos are sucked up into a very thin plastic tube (catheter) and the tip of the catheter is carefully inserted into the uterus. The embryos are then injected into the uterus in a drop of nutrient solution. The position of the catheter is monitored by ultrasound and one can often see the position of the egg in the uterine cavity. A *maximum of two* embryos are transferred, even though more may be available. If we transfer two embryos, there is a good chance of pregnancy being established. If there are many embryos, those that appear to have the best chance of developing a pregnancy are chosen, i.e. those which have divided most, those that have the healthiest looking cells etc.

RISKS
There is *minimal risk* associated with hormone stimulation and egg removal. Treatment is carried out on an outpatient basis. Monitoring with hormone analyses and ultrasound checks are intended to avoid overstimulation of the ovaries.

CONTROL FOLLOWING EMBRYO TRANSFER
One prerequisite for the egg to "stick" is that the uterine membranes are receptive. This is hormone-controlled. Therefore, we normally prescribe *hormone injections* (Progesteron). It is important to detect at an early stage if the IVF treatment has resulted in a pregnancy since the risk for ectopic pregnancies is slightly greater than normal. Of those women who have become pregnant with IVF, 2-3% can be expected

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to have ectopic pregnancies. This is due to the fact that women who undergo IVF often have damaged oviducts where the embryo can get stuck. Therefore, blood tests are taken during the period following embryo transfer. If an increased level of hCG (the pregnancy hormone) is detected, we then prescribe an ultrasound examination soon thereafter to check that the pregnancy is in the uterus as it should be. In the unlikely event of an ectopic pregnancy, treatment can begin before the woman experiences any discomfort.

CHANCES OF SUCCESS

At Huddinge Hospital Gynaecological Clinic, the chances of actually having a child have remained stable at 22-25% per started treatment over the last six years. Unfortunately, the most likely result of a single IVF treatment is not a pregnancy. However, within a series of three IVF treatments, we expect to succeed in about 50% of the cases. Before the couple start the first IVF treatment, they should consider whether the often tough IVF treatment is worth the effort, considering that many treatments fail.

The likelihood of giving birth to a defective child after IVF treatment is *no greater* than for corresponding fertile groups. However, the risk, or the chance, for twins, is *significantly higher* if IVF results in a pregnancy. In our clinic, one pregnancy in five has resulted in twins. No triplet pregnancy has been established the last three years.

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FREEZING OF EMBRYOS

Often, many more than the two embryos that are transferred to the uterus are produced. We can now *freeze extra embryos*. One prerequisite for this is that the embryos are of "good quality", i.e. they look very even and healthy under the microscope. If the treatment in question does not result in pregnancy, frozen embryos can be used for the next treatment. After thawing the frozen embryos, they can be introduced during a normal menstruation cycle, two days after ovulation, i.e. the treatment is much simpler. Embryo freezing can be carried out for 10-20% of couples. More information will be given on your first visit here.

PSYCHOLOGICAL ASPECTS

Before a couple has come as far as IVF treatment, they have often wandered a long and difficult route via examinations and treatments that have meant much waiting and swings between hope and desperation. The sorrow of not being able to have one's own biological child can be hard to handle. Sometimes, the situation affects the *couple's relationship and sexuality*. Even if childlessness is the combined problem of the couple, one of the two can experience the situation as harder than the other. People have different ways of handling their difficulties, sadness and disappointments and sometimes it can be difficult to understand each other's reactions.

IVF treatment means new hope. However, perhaps both parties are not sufficiently in balance for the demanding treatment. Perhaps neither one is prepared to handle the disappointment that many will experience. The parties need to talk with each other about their feelings. They need to try and express their fears and expectations. The attitude to adoption or a continued life without children also needs to be discussed.

Sometimes one can feel that relatives and friends do not understand the problems associated with childlessness. One may decide not to inform them. If one has the strength to talk to them about the situation and feelings, they can often provide significant support.

Sometimes it is helpful to talk to a complete outsider. At Huddinge Hospital Gynaecological Clinic and, for patients from abroad, at the local hospital, social workers are available for supportive discussions. One can also contact IRIS (Association for the Infertile in Sweden) which can provide advice and support. Their address is Box 34, 860 35 Söråker, telephone 060-408 64, telefax 060-408 74.

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ID	Level of lesion and ASIA impairment grade	Sperm count	% motile	% normal morphology
1	C4 A	11.4	5.0	5.0
2	C5 A	342.0	9.0	1.0
3	C5 A	420.0	28.0	54.5
4	C5 C	473.8	10.0	27.0
5	C5 C	327.2	18.1	62.0
6	C6 A	94.6	7.0	1.0
7	C6 A	0.0	0.0	0.0
8	C6 B	160.4	31.8	51.5
9	C6 B	632.5	10.0	45.0
10	C6/C7	978.0	7.7	58.0
11	C6/C7 A	221.1	23.3	56.5
12	C6/C7	0.0	0.0	0.0
13	C7 A	50.0	1.0	20.5
14	C7 A	205.4	22.4	45.3
15	C7 A	185.9	17.4	61.5
16	C7 B	470.0	10.0	22.0
17	C7 B	39.0	13.8	7.5
18	Th3 A	27.6	88.1	46.5
19	Th3 A	108.5	26.2	19.5
20	Th4 A	70.6	28.0	1.0
21	Th4 A	24.5	36.0	34.5
22	Th6 A	439.0	13.0	45.0
23	Th6 A	409.6	9.5	49.5
24	Th6 A	12.6	10.0	13.5
25	Th7 A	210.0	32.0	37.0
26	Th7 A	0.0	0.0	4.0
27	Th8/Th9 A	497.3	5.0	1.0
28	Th9 A	150.0	5.0	30.0
29	Th9 A	109.8	14.6	27.0
30	Th9 B	182.3	43.0	48.0
31	Th9 C	267.1	17.3	15.0
32	Th10 A	0.0	0.0	28.5
33	Th10 A	0.0	0.0	0.0
34	Th10 A	0.0	0.0	0.0
35	Th10 B	7.0	30.0	4.0
36	Th11 A	694.0	14.0	55.5
37	Th11 B	129.6	9.9	58.5
38	Th11 C	312.8	6.0	46.0
39	Th12 A	34.5	11.5	67.0
40	Th12 A	6.0	10.0	22.0
41	Th12 A	94.1	8.0	18.3
42	Th12 B	170.0	5.0	6.0
43	Th12 C	96.0	1.0	12.0
44	L3 D cauda	289.6	32.0	60.8
45	L3/L4 B	38.5	3.9	34.0

If more than one semen retrieval has been performed, the mean value is entered.