Iatrogenic damage to male reproductive function

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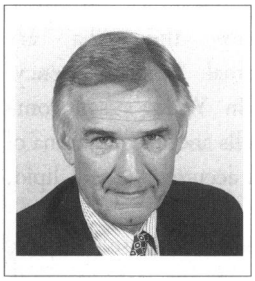

Bill Hendry qualified in medicine from the University of Glasgow in 1961 and trained in urology at St Peter's Hospital in London. He has been a consultant urologist at St Bartholomew's and Royal Marsden Hospitals since 1973 and had an honorary consultant attachment to Chelsea Hospital for Women, during which time he developed a special interest in the management of male infertility. His work at Bart's and Royal Marsden Hospitals has concentrated mainly on urological cancer, but with a continuing interest in male infertility. He is Vice-President of the British Association of Urological Surgeons and has edited the last five editions of *Recent Advances in Urology*: he is co-editor of the *Textbook of Genito-Urinary Surgery* and co-editor of the *British Journal of Urology*.

As President of the Section of Urology, Royal Society of Medicine, in 1994/1995, he has: encouraged interdisciplinary collaboration (the Section has held combined meetings with the Sections of Obstetrics & Gynaecology, Oncology, Radiology and Paediatrics); developed Commonwealth ties; and encouraged participation of the young (the final meeting of the Section held in North Wales includes the Geoff Chisholm Registrar's Communication Skills Prize).

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Tread softly because you tread on my dreams (W B Yeats)

INTRODUCTION

In the complex, rather fragile relationships that exist between men and women, reproduction plays a pivotal role—not only for the self esteem and confidence of the man, but also in the dreams and expectations of the woman. In marriage, initial happiness can turn to sadness and disillusionment if the man's sexual function is impaired or damaged. Such damage, either inadvertent or inevitable, occurring as a result of medical or surgical treatment of an unrelated complaint is the subject of this review. A man's reproductive system may be considered as starting in the testicle with spermatogenesis. The product is despatched through epididymis and vas to be stored in the ampulla and seminal vesicles. Delivery requires erection of the penis and ejaculation from the urethra for completion of the process. Each part of this path is vulnerable, and each will be considered to define the risks to which they are exposed during medical therapy.

THE TESTICLES

Susceptibility of the testicles to iatrogenic damage starts in the uterus. The male offspring of women given diethylstilboestrol during pregnancy to prevent miscarriage were found to have hypotrophic genitalia and impaired seminal analysis significantly more often than those whose mothers received placebo[1]. Furthermore, there is some evidence that the increasing incidence of cryptorchidism and testicular tumours, and a steady decline in average sperm concentration observed in men in Northern Europe, may have their origins in exposure to excessive amounts of maternal oestrogen *in utero*[2,3].

Spermatogenesis is very sensitive to drug therapy. Sulphasalazine provides perhaps the best example of a drug therapy that was identified, modified and ultimately eliminated in order to minimize its genital side effects. Initial enquiries in 1977 met with bland reassurance. However, investigation showed that replacement of Salazopyrin with other drug therapy lead to normalization of the sperm concentration and subsequently to pregnancies in the female partners[4,5]. Detailed investigations revealed that of the two components of sulphasalazine, sulphapyridine and 5-aminosalicylic acid (5-ASA), sulphapyridine appeared to be causing the problem[6], and substitution of 5-ASA for sulphasalazine rapidly lead to normalization of sperm output[7].

Testosterone therapy leads to suppresion of gonadotrophins, and ultimately to azoospermia[8]. The current vogue for testosterone supplements to treat the so-called male menopause may improve libido, but it diminishes fertility and this may come as a disappointment to middle aged men who have taken on a young partner. Similarly, anabolic steroids used by body builders may lead to impairment of spermatogenesis.

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Amongst antibiotics, nitrofurans, aminoglycosides and macrolides such as erythromycin may lead to spermatogenic arrest in rats, and impaired sperm motility in humans[9]. The calcium channel blocker nifedipine has recently been shown to interfere with the acrosome reaction causing failure of *in vitro* fertilization[10]. Other drugs implicated in impairment of fertility include cimetidine, colchicine, anticonvulsants, alcohol, cannabis and opioids[11].

Many men presenting with testicular tumours are infertile, but it is not always clear whether this antedated the development of the tumour, or was due to the tumour itself, or resulted from its treatment[12]. At presentation, only one-quarter of these men have semen quality good enough to permit cryopreservation[13]. One-quarter have severe irreversible impairment of spermatogenesis demonstrable on testicular biopsy[14]. Amongst the remainder, there is the potential for recovery of normal spermatogenesis. It is, therefore, very important to limit toxicity of treatment in these young men.

The deleterious effects of ionizing radiation on spermatogensis have been well documented. Oligoozoospermia follows a testicular dose of 50–78 cGy, and azoospermia is likely after doses above this level; recovery after a dose of less than 100 cGy takes 0–18 months[15]. By shielding the remaining testis during para-aortic radiation, the dose can be kept to less than 50 cGy and recovery of spermatogenesis is likely, whereas permanent azoospermia is inevitable following scrotal irradiation[16]. This is the reason for avoiding a scrotal incision when dealing with testicular tumours, although these strict caveats may be less important than they were, now that effective chemotherapy is available. Indeed, local recurrence was uncommon on surveillance after scrotal interference in a series of men with testicular tumours[17].

Chemotherapy agents vary in their effects on spermatogenesis: chlorambucil, cyclophosphamide and procarbazine are severely damaging, and recovery is likely to be poor; cisplatinum, vincristine, cytosine arabinoside, 6-mercaptopurine and doxorubicin are moderate in their effects and prospects for recovery are good[18]. The combinations used for treatment of metastatic testicular tumours such as bleomycin-etoposide-cisplatinum (BEP) have a good chance of recovery of spermatogenesis after a period of 1–2 years[19]; the prospects for the patient with Hodgkin's disease, on the other hand, are poor[20]. Cryopreservation of semen should be offered when treatment is likely to lead to irreversible damage, and excellent results can be obtained with artificial insemination[21].

THE EPIDIDYMIS AND VAS

Hold up in the heads of the epididymes is the commonest cause of obstructive azoospermia in the UK, and the results of surgical reconstruction are poor. These capital blocks are associated with chronic chest disease in three-quarters of the patients, an association known as Young's syndrome[22]. The lesions are symmetrical and the transition between distended and empty tubules coincides with the change from ductuli efferentes in the head of the epididymis to ductus epididymis in the body. The ciliated columnar epithelium lining the ductuli efferentes is similar to that lining the nasal and respiratory passages[23]. Mucociliary clearance in these patients is defective, and since the cilia are ultrastructurally normal with normal beat frequency, increased viscosity seems likely[24]. In Young's syndrome there is excess lipid in the epithelial cells and in the lumina of the ductuli efferentes with abnormal accumulation of lipid, which appears to impair flow[25].

There was a definite past history of pink disease (mercury intoxication) in childhood in 10% of our patients with Young's syndrome. Both pink disease and Young's syndrome became much less common in men born after 1955, when mercury containing teething powders were withdrawn in the UK. It is, therefore, most likely that exposure to mercury in childhood had a part to play in the aetiology of this condition[26]. Disappearance of this condition in men with azoospermia should lead to a significant improvement in the results of epididymo-vasostomy, which might approach the success rates observed in countries such as the USA where the sale of calomel containing medications has been discouraged for over 50 years.

Surgical damage to the testicular outflow tracts is not uncommon. Part or all of the epididymis may be removed during excision of epididymal cysts or painful nodules; similarly, the vas may be interrupted during groin surgery especially in infancy or childhood: in a recent review of 50 such cases, the causes of the blocks included hernia repair (29 cases, average age of surgery 6 years), hydrocele operations (six cases), epididymal cyst removal, epididymal biopsy, and other groin or genital operations or injuries[27]. Although unilateral testicular obstruction does not necessarily cause infertility, it may do so: for example, if the function of the contralateral testis is impaired, the total sperm output may be reduced to such an extent that the man becomes infertile. Furthermore, obstruction to the testicular outflow may result in formation of antisperm antibodies, due to the absorption of spermatozoa via the lymphatics[28] and their deposition in the abdominal lymph nodes[29]. Experimental unilateral vasoligation stimulated antisperm antibody production in animals[30] and this has been observed in a man with testicular obstruction[31]. Impairment of fertility was also observed after unilateral vasectomy in mice that are known to be strong responders to antigenic stimuli[32]. Subfertile men who suffered unilateral genital tract injury in childhood have been found to have significantly higher antisperm antibody titres than those

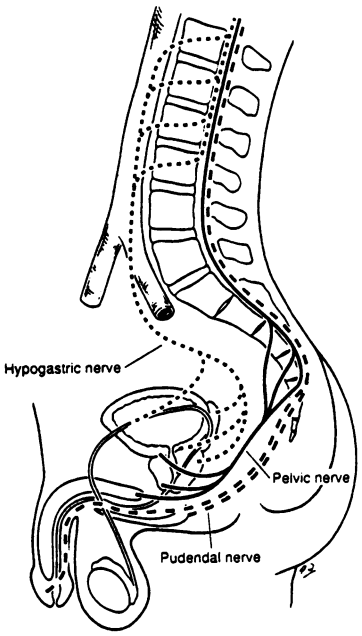

Figure 1 **Innervation of internal male genitalia. Ejaculation is controlled by the sympathetic nerve supply (T12–L3) which produces contraction of the prostate, vesicles and vasa, with bladder neck closure. Erection is controlled by the parasympathetic supply (S2–S4) which innervates the corpora cavernosa, prostate, base of bladder and bladder neck. The somatic (pudendal) nerves run to the perineal muscles which complete emission, and to the penile urethra and corpus spongiosum**

with bilateral injuries, indicating that unilateral injury without antibody production is probably compatible with maintenance of normal fertility[33]. Men with normal spermatogenesis and antisperm antibodies with unilateral testicular obstruction form a favourable group in whom the opportunity of improving their fertility by correcting this damage should not be missed[27].

EJACULATORY DUCTS

Impaired sexual function is a well recognized complication of excision of the rectum in men[34]. With imperforate anus, the perineal dissection necessary for the pull through procedure, particularly in the presence of a rectourethral fistula, can damage the ejaculatory ducts or vasa deferentia and cause testicular obstruction. Amongst 19 infertile men after surgery for imperforate anus in infancy, we found that seven had no ejaculate, 10 were azoospermic, one severely oligozoospermic and only one had a normal sperm concentration although in a small volume of ejaculate. Investigation revealed that both vasa were blocked in five men, and one vas in a further eight, apparently as a result of the original operative procedure. With the unilateral blockage, there were various abnormalities on the contralateral side including postinflammatory obstruction after epididymitis, or congenital malformations associated with absent or ectopic kidney[35]. Excision of seminal vesicle cyst can also lead to ejaculatory duct obstruction[36].

EJACULATION AND ERECTION

The innervation of the internal male genitalia is complex (Figure 1)[37]. Sympathetic inflow is by the hypogastric plexus which is derived from T12 to L3: this stimulates contraction of the prostate, vesicles and vasa along with partial bladder neck closure producing ejaculation, and division of these nerve fibres leads to loss of ejaculation. Parasympathetic innervation of the corpora cavernosa, prostate, base of bladder and bladder neck is from the S2 to S4 roots via the pelvic nerves: division or injury of these nerves (for example during radical prostatectomy) leads to loss of erection. The final act of ejaculation is via the somatic muscles surrounding the urethra which are innervated via the pudendal nerve.

Ejaculation

Ejaculation is an essential part of the reproductive process without which transfer of spermatozoa from male to female partner cannot naturally take place. Loss of this function has a severe deleterious effect on sexual and marital relationships[38]. Now that most patients are cured of testicular tumours every effort must be made to minimize toxicity and eliminate side effects[39]. Furthermore, failure to warn a patient of alteration in sexual or reproductive function following treatment of a curable cancer may very well be interpreted as negligent, particularly if every care is not taken to reduce the likelihood of such side effects occurring[40].

Many studies have shown that the chief cause of loss of ejaculation is paraaortic lymph node dissection and this has been known for many years[41]. Up to three-quarters of these patients lost antegrade ejaculation after bilateral retroperitoneal lymph node dissection, and detailed studies showed that many not only lost ejaculation but also suffered diminished libido, difficulty with orgasms, and in some cases, erectile dysfunction[42]. As a result of careful anatomical studies, the technique of retroperitoneal lymph node dissection has been modified so that antegrade ejaculation is maintained in 70–90% of patients[43,44]. The technique of nerve sparing retroperitoneal lymphadenectomy is however painstaking and prolonged and may take anything up to 4–5 h to complete. Some temporary loss of ejaculation is not uncommon but generally recovers over the months following the procedure. Experience at the Royal Marsden Hospital showed that retroperitoneal lymph node dissection for early stage non-seminomatous germ cell tumours of testis is unnecessary[45,47]. Of more than 300 such patients treated by surveillance to date, only one has died and 55 have successfully produced children (unpublished observations). It is therefore hard to understand why some surgeons persist in carrying out such a damaging operation for early stage disease. However, paraaortic lymphadenectomy may have to be done for the residual nodal masses in the paraaortic region which persist in about 25% of patients after completion of chemotherapy[47]. Multivariate analysis of

231 such men indicated that complete removal optimized survival, and histological examination of the excised mass revealed that undifferentiated tumour was present in 21% of patients, who had a significantly worse prognosis[48]. After retroperitoneal lyphadenectomy under these circumstances, loss of ejaculation occurred in 22% of our 186 patients who were available for study[49]. The larger the size of the mass removed, the more likely the patient was to have ejaculatory failure, and removal of bilateral masses was more likely to result in loss of ejaculation than unilateral masses. However, with the introduction of nerve sparing dissection in 1984, there was a significant reduction in loss of ejaculation from 36% of patients operated on before then to 16% of those thereafter. Drug treatment for loss of ejaculation is not very successful[50] but electroejaculation can produce spermatozoa for insemination[51].

It is well known that retrograde ejaculation often occurs after prostatectomy, and to a lesser extent after bladder neck incision, but it remains absolutely essential that this is made clear to patients before operation, and written down as part of their informed consent to the procedure[52]. In fact, spermatozoa can be retrieved from post-orgasmic urine by centrifugation, resuspended and used for insemination with success: cumulative pregnancy rate of 72% at 6 months was achieved amongst 14 couples treated by Scammell[53].

Erection

Although there are no exact figures for the incidence of impotence in the general population, it is estimated that around 10% of those in the 6th decade, 20% in the 7th decade, 30–40% in the 8th decade and over half of those in the 9th decade have some difficulty with erections[54]. This has been attributed to a gradual decline in total plasma testosterone with increase in sex hormone binding globulin, leading to a reduction in free testosterone[55]. Added to this natural attrition are the side effects of drugs that are given with increasing frequency as people get older. Amongst antihypertensive drugs, erectile impotence is fairly common with thiazides (10–20%), spironolactone (5–40%), and propranolol (10–15%), but is rather rarer with atenolol, prazosin and ACE inhibitors. Methyldopa can lead to loss of libido and delayed ejaculation as well as erectile difficulties. The prevalence of both impotence and failure of ejaculation is higher in treated hypertensive patients than in matched controls. While psychotropic drugs are associated with sexual dysfunction in a high proportion of patients, on the other hand, it is not always clear whether this is due to the drugs or to the underlying illness. Nevertheless, it is clear that up to 40% of patients taking monamine oxidase inhibitors experience sexual dysfunction, and the tricyclic antidepressants cause reduced libido and impotence in up to 20% of patients. Selective serotonin reuptake inhibitors are less often associated with such side effects, with fluvoxamine in particular having the lowest rate[56].

The incidence of loss of erection after prostatectomy depends on erectile function preoperatively: amongst those who started out fully potent, less than 5% become impotent after operation; by comparison, of those who are only partially potent, 10–37% become completely impotent and more have potency significantly reduced after operation[57,58]. Factors predicting no deterioration in sex life after transurethral resection include good general health, normal preoperative sex life and, perhaps surprisingly, emergency admission[59]. In a recent survey, informed consent to transurethral prostatectomy was found to include written reference to these facts in only one-third of patients irrespective of whether the men were married, single or widowed[52]. Recent court cases have indicated that it may be prudent to make clear the possibility of these potential complications, and record the fact that this has been done carefully, if future litigation is to be avoided.

After radical prostatectomy, ejaculation is bound to be lost since the seminal vesicles are removed with the prostate gland, and erectile impotence was the rule until Lepor *et al.*[60] showed where the nerves ran behind the prostate gland and Walsh developed an operative technique to preserve them[61]. As a result, most men now preserve potency after this operation, although the exact incidence depends on age, varying from 91% of those aged 50 or less, through 75% of those 50–59, and 58% of those 60–69, to 25% of the few undergoing this operation who are aged 72 years or more[62]. Similar figures have been reported from other specialist centres in the USA[63], but national Medicare experience (1988–1990) indicated that only 11% of men actually have erections firm enough to permit intercourse although this rises to 28% with appropriate treatment[64]. Similarly, Jonler *et al.*[65] found that only 16% of 93 men had erections firm enough to have penetrative intercourse compared to 84% preoperatively. After radical radiotherapy for carcinoma of the prostate, Banker[66] found that 73% of those who had intercourse more often than three times a month before treatment could still achieve a full erection 8–12 months after receiving 65–70 Gy in 6.5–8 weeks, as well as 43% of those who initially had intercourse less frequently. It is reasonable to expect these figures to be made available to the younger man with early carcinoma of prostate who has to choose which treatment to submit himself to, particularly now that more and more potentially curable cases are being picked up by PSA (prostate specific antigen) screening.

Advanced prostatic carcinoma responds well to androgen ablation such as orchidectomy, to oestrogen therapy, or to endocrine manipulation with an LHRH (luteinising hormone releasing hormone) analogue such as goserilin, but sexual function is inevitably severely impaired. With a selective antiandrogen such as flutamide, by contrast, most patients

show a good disease response and those who are potent retain their potency on treatment[67]. Ongoing prospective controlled trials have shown that flutamide was as effective as orchidectomy as judged by time to progression and overall survival provided that the serum PSA was not grossly elevated (not more than 120ng/ml) at entry (Boccon-Gibbod, personal communication). It is possible that increasing awareness of the importance of sexual function may allow this disease to be treated equally effectively but with less side effects in future.

CONCLUSIONS

After life itself, fertility is probably the most highly prized human possession. Yet, while cure of the individual naturally demands priority, relatively little attention is paid to the effects of treatment on reproductive function. Perhaps this is because it is so complex, so difficult to measure satisfactorily. Life can be quantified by 5 year survival rates, but fertility involves not one but two individuals and their interaction. Worse, one partner may be, at the time of treatment, only the subject of romantic dreams: but consideration must be given to the day when dreams come true. The new found partner has every right to expect that due care was taken of the fertility and sexual function of her loved one. There was a day when the old attitude amongst doctors was a bluff 'well you can't have sex in a coffin, you know'. Increasingly successful treatments, a more open society and legal precedent all now demand that reproductive function and future fertility are kept in mind, and fully discussed with both patient and relatives before, during and after treatment.

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