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FEMALE GENUINE STRESS INCONTINENCE -
AN OBJECTIVE STUDY OF ASPECTS OF ITS ACTIOLOGY,
INVESTIGATION AND CONSERVATIVE TREATMENT

by

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ABSTRACT

FEMALE GENUINE STRESS INCONTINENCE -
AN OBJECTIVE STUDY OF ASPECTS OF ITS AETIOLOGY,
INVESTIGATION AND CONSERVATIVE TREATMENT

By P.D. Wilson

The management of female urinary incontinence suffers frequently from a lack of objective criteria both for its assessment and the evaluation of treatment. Genuine stress incontinence is the commonest type of incontinence in non-geriatric female patients and this thesis is the report of an objective study which has examined aspects of its aetiology, investigation and conservative treatment. Firstly, regarding aetiology, the theory that defects in the posterior pubo-urethral ligaments predispose to genuine stress incontinence was examined by comparing the ligaments of incontinent patients with those from normal women using techniques of neurohistochemistry and electron microscopy. The specimens from the incontinent patients were identical in morphology, histochemistry and fine structure to those from the control females indicating that altered morphology of the posterior pubo-urethral ligaments is unlikely to be an aetiological factor in genuine stress incontinence. The term "ligament" may be a misnomer as these structures were also shown to contain a marked smooth muscle component which was associated with nerves, the enzyme content and fine structure of which were similar to those believed to represent cholinergic nerves.

Three studies were carried out which examined aspects of investigation; two looked at diagnosis and one at the assessment of leakage. In the diagnosis of genuine stress incontinence the object is to identify urethral incompetence in the absence of abnormal detrusor activity (instability), which can usually be excluded by cystometry. The first of these studies examined retrospectively the cystometrograms of 316 consecutively investigated women and confirmed the importance of studying postural influences on cystometry as 50% of the cases of detrusor instability would have remained undetected if only supine tests had been performed. This postural effect was also shown to be related to the age of the patient as supine cystometry detected a higher proportion of cases of detrusor instability as age increased. The second study assessed the accuracy of the newer Fluid Bridge Test compared with cystourethrography in detection of urethral incompetence. This test produced better correlation with cystourethrography when performed in the erect rather than supine position however, overall, it was less reliable in the diagnosis of genuine stress incontinence. An assessment of the Uriilos System (electronic nappy for quantifying leakage) was carried out in the third of these investigative studies and showed that although it detected minimal incontinence, because of major problems of under- and over-recordings between nappies and poor reproducibility between packs of nappies this System was not, as yet, a reliable method of quantifying incontinence.

Using these investigative techniques, further studies

were performed to assess the value of physiotherapy and the role of oestrogens in the conservative treatment of genuine stress incontinence. Four groups of fifteen patients were treated prospectively with a variety of physiotherapy techniques (Pelvic Floor Exercises (PFE) in Hospital, PFE + faradism, PFE + interferential therapy and PFE at home) and assessed subjectively and objectively. Physiotherapy was shown to be a useful treatment for selected incontinent patients as two-thirds of the hospital treated patients experienced marked or moderate subjective improvement (compared with less than one-third of the home treatment group) and this change continued in the majority when assessed at six months. There was little subjective or objective difference between each of the three hospital based treatment groups. Statistical analyses showed there were significant improvements in the objective parameters in the 45 actively treated patients. Patients who experienced success with physiotherapy, were shown to be younger, had less frequently a history of previous pelvic floor surgery, had less urethral incompetence at cystourethrography and had less major degrees of incontinence as assessed by pad changes and the Urilos nappy in comparison to their "failure" counterparts.

Oestrogen receptors were identified for the first time in the human female lower urinary tract predominantly in the middle and distal thirds of the urethra, thus providing objective evidence that the urethra is an oestrogen "target" organ.

To evaluate the clinical significance of these receptors in genuine stress incontinence, a double blind prospective study was then performed in which 36 post-menopausal incontinent patients received either 3 months cyclical treatment with piperazine oestrone sulphate or a matching placebo. There was a significant reduction in leakage in the oestrogen treated patients after 6 weeks of therapy. However on account of the definite placebo response, there was no significant difference between the two groups on completion of the course. In view of the known risks of oestrogen therapy, it was concluded that its use in genuine stress incontinence would appear to be limited.

PREFACE

Urinary incontinence is a distressing and often incapacitating condition, which in addition to its medical importance has significant social implications. Genuine stress incontinence (the involuntary loss of urine when intravesical pressure exceeds the maximum urethral pressure in the absence of detrusor activity), is the commonest type of incontinence in non-geriatric female patients (Moolgaoker et al, 1972). An important factor in the aetiology of this condition is the position of the proximal urethra in relation to the pelvic floor musculature; if the urethra comes to lie below the pelvic floor, intra-abdominal pressure increases (for example during coughing) are incompletely transmitted to it thus pressure gradients are altered and genuine stress incontinence may result (Enhorning, 1961).

The pubo-urethral ligaments, in particular those posteriorly, are considered to support the proximal urethra and prevent its descent (Zacharin, 1972). It has been suggested that defects of these ligaments may predispose to genuine stress incontinence (Krantz 1951, Zacharin 1963, Milley and Nichols 1971). Modern neurohistochemical techniques and electron microscopy have given a new insight into the structure and innervation of the urethra and bladder (Gosling, 1979), but until now these techniques have not been applied to study the microstructure and possible innervation of the posterior pubo-urethral ligaments.

In general, female urinary incontinence has been assessed subjectively by history and clinical examination. However these methods have limitations and the clinical application of urodynamics (which provides an objective assessment of the urinary tract) has improved significantly diagnosis and resulted in a more rational approach to treatment. In the diagnosis of genuine stress incontinence, since the basic problem would appear to be a defective urethral closure mechanism, the object is to identify this urethral incompetence in the absence of abnormal detrusor activity (instability). The latter can usually be excluded by cystometry (measurement of intravesical pressure changes in relation to volume) while urethral incompetence is commonly detected by cystourethrography (Whiteside 1973), but more recently by the Fluid Bridge Test (Brown and Sutherst 1978) by inference from pressure relationships between the bladder and urethra. As well as diagnosis, assessment of leakage is an important aspect of investigation and the Urilos System (electronic nappy) has been devised to quantify incontinence, (James 1971).

It is accepted generally that surgery is necessary to treat severe genuine stress incontinence and that the retro-pubic approach is preferable usually to the vaginal route (Hodgkinson, 1970). The treatment of mild to moderate incontinence is less certain and conservative measures should be tried initially as they are frequently helpful (Brown 1977). Also there are some patients for whom surgery is inappropriate. The conservative measures

include physiotherapy and oestrogen treatment.

The value of physiotherapy has not been objectively assessed. Kegel (1951) described the use of pelvic floor exercises and he reported a cure rate of over 80%. Similar results have been recorded by Jones and Kegel, (1952) and by Jones (1963). Striated muscle stimulation by faradism (Moore and Schofield 1967) and interferential therapy (McQuire 1975) have been used as an adjunct to pelvic floor exercises. However, in all these studies there was little or no objective assessment of the type and degree of incontinence nor of the results of treatment.

There is also no agreement on the role of oestrogens in genuine stress incontinence. The female lower urinary and lower genital tracts have similar embryological origins arising from the primitive urogenital sinus (Hamilton and Mossman, 1972) and the lower urinary tract appears to be sensitive to both oestrogen and progesterone (Zuckerman, 1940, Smith 1972, Caine and Raz 1973). However there are no published reports of the demonstration of either of these hormone receptors (specific cytoplasmic steroid binding proteins) in this site in the human. Oestrogen deficiency leads to atrophy of the urethral mucosa (Smith 1972) and is believed to be a contributory factor in genuine stress incontinence (Hald 1975, Stanton 1977). Studies have been performed to evaluate oestrogen therapy for incontinence (Caine and Raz 1973, Walter et al 1976) but the data is conflicting.

OBJECTIVES OF THESIS

This thesis seeks to examine aspects of aetiology, investigation and conservative treatment of female genuine stress incontinence using objective criteria:

1. To examine the role of the posterior pubo-urethral ligaments in the aetiology of incontinence by comparing the ligaments in continent females with those in genuine stress incontinent patients using the techniques of standard histology, neurohistochemistry and electron microscopy.
2. To review critically the methods of urodynamic investigation of genuine stress incontinence and also:
 - a) To evaluate postural cystometry and the effect of age in detecting detrusor instability.
 - b) To assess the accuracy of the Fluid Bridge Test compared with cystourethrography in the diagnosis of genuine stress incontinence.
 - c) To assess the Uriilos System.
3. To assess the value of physiotherapy with/without faradism or interferential therapy in the treatment of genuine stress incontinence.

4. To study the role of oestrogens in genuine stress incontinence by:

- a) Estimating the level of cytosol oestrogen and progesterone receptors in the female lower urinary tract.
- b) Assessing the effect of piperazine oestrone sulphate (Harmogen) on post menopausal women presenting with genuine stress incontinence.

CHAPTER 1

INTRODUCTION

AND

REVIEW OF PREVIOUS WORK

1.1 FEMALE LOWER URINARY TRACT

A brief account of the structure and function of the female lower urinary tract is presented with emphasis on the anatomy which is relevant to the proposed studies. The mechanisms of continence are described and the causes of female incontinence are classified together with their incidence in the population of patients studied.

1.1.1 Structure of the Female Lower Urinary Tract

Detrusor Smooth Muscle

The bladder is composed of smooth muscle (detrusor) and is traditionally described as having three layers, an outer longitudinal layer, middle circular and inner longitudinal layer. However, recent studies (Gosling and Dixon, 1975) have shown that the detrusor muscle consists of numerous interlacing bundles which connect with each other in an intricate fashion; this arrangement results in the formation of a complex meshwork of muscle which contracts as a single unit. The bladder is described by bioengineers as a viscoelastic structure in which the tissue elongates as filling occurs although its structural linkages remain unchanged (Coolsaet et al, 1975; Van Mastrigt et al, 1976).

Trigone

The trigone consists of two layers, superficial and deep, both of which are derived from mesoderm. The deep trigonal muscle is considered to be the postero-inferior

part of the detrusor (Gosling 1979) since its morphology, histochemistry and innervation is indistinguishable from that of the detrusor proper. The superficial muscle layer of the trigone consists of thin, closely packed bundles (Bell's muscle) which are continuous with the inner longitudinal muscle of the intramural ureter (Donker 1976). The superficial trigonal muscle extends into the proximal urethra (Gosling 1979) but debate continues concerning the relationship between detrusor and urethral smooth muscle. Many authors state that the urethral muscle is a downward extension of the detrusor (Lapides, 1958, Woodburne 1960, Tanagho and Smith 1966), however using neurohistochemical techniques Gosling and Dixon (1975) have shown that the detrusor and urethral smooth muscles are separate.

Female Bladder Neck and Urethra

The female urethra is a hollow elastic tube, the length of which is 3.5 cm with a range of 1.5 to 5 cm, (Roberts and Smith, 1976). The urethra is lined proximally by pseudostratified transitional epithelium which is continuous with that of the bladder and distally by stratified squamous cells which continue into the introitus. The latter epithelium is similar to that of the vagina and it may represent the part of the urethra which is derived from the definitive urogenital sinus (Hamilton and Mossman, 1972). The level at which the epithelium changes from transitional to squamous type varies as the latter has been found within the trigone (Packham, 1971).

The urethra has two muscle layers. The relatively thin inner layer consists of small bundles of smooth muscle which run obliquely or longitudinally throughout the urethral length (S.M. - Figure 1A). Gosling (1979) has not found any evidence of a sphincteric arrangement of smooth muscle (internal urethral sphincter) in the female bladder neck and proximal urethra in contradiction to earlier anatomical studies, (Uhlenhuth, 1953, Hutch, 1972). He suggests that smooth muscle contraction shortens and widens the urethra during micturition and its contribution to urethral closure (hence continence) is probably small.

External to the smooth muscle are the striated fibres that constitute the external or distal urethral sphincter (E.S. - Figure 1A); these are circularly disposed and are most abundant along its middle third. The striated muscle extends along and completely surrounds the urethra although the dorsal part between urethra and vagina is relatively thin. This intramural striated muscle is separated from the adjacent but somewhat remote pelvic floor musculature by a collagenous layer (see below).

The muscle cells of the external sphincter are unusual in that they are on average less than half the diameter of the cells in the peri-urethral striated muscle (Gosling and Dixon 1977). Functionally, they are "slow twitch" fibres capable of sustained contraction over relatively long periods and their tone is thought to

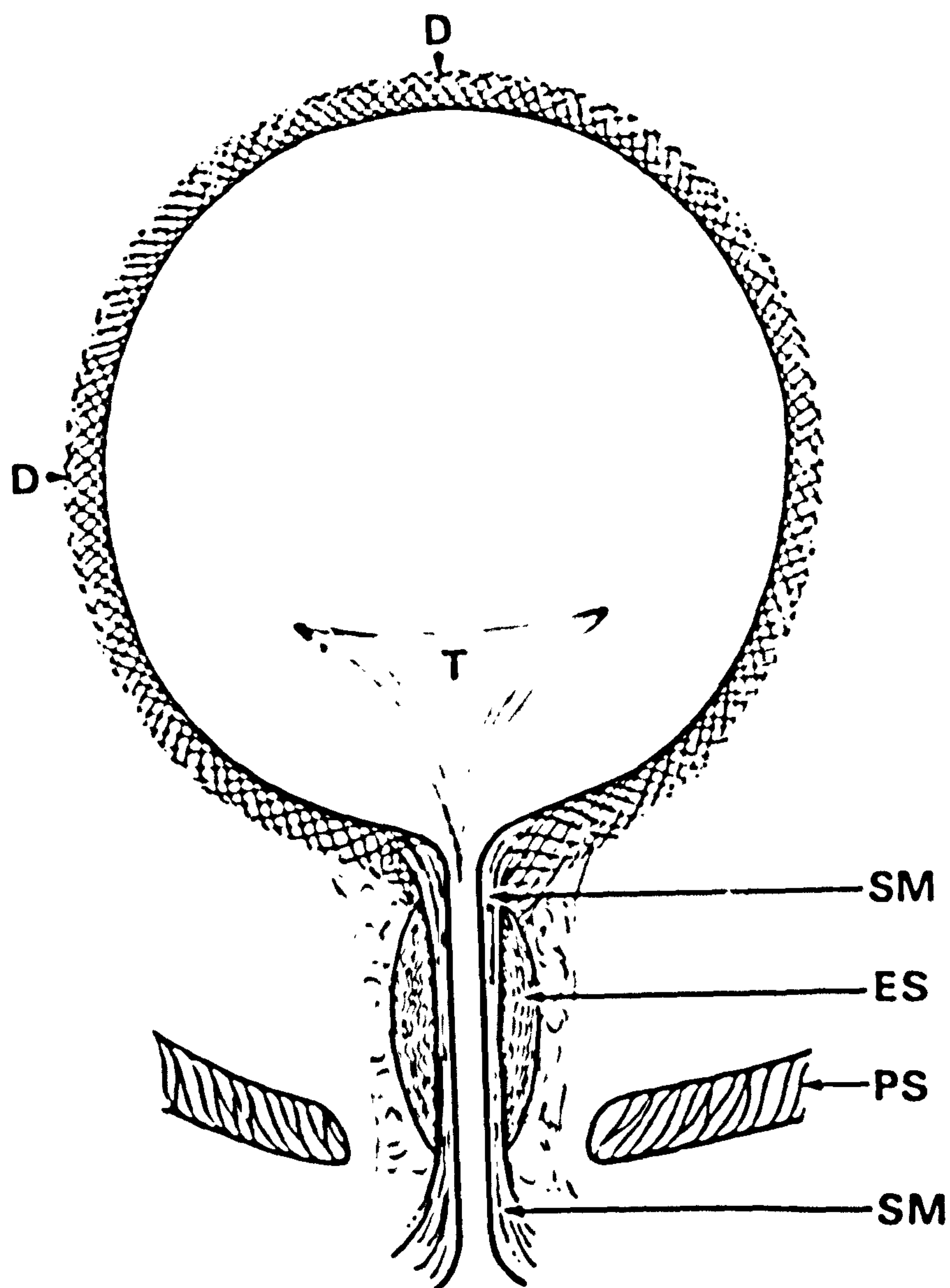


FIGURE 1A - Coronal Section of Female Lower Urinary Tract.

Key: D - Detrusor Smooth Muscle
 T - Trigone
 SM - Urethral Smooth Muscle
 ES - External Striated Sphincter
 PS - Periurethral Striated Muscle

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contribute to urethral closure and hence continence (Gosling, 1979).

In addition to smooth and striated muscle the urethra contains much collagenous and elastic tissue which is thought also to contribute albeit passively to urethral closure (Woodburne, 1960).

Pelvic Floor

The pelvic floor consists of striated muscle and fascial planes which are perforated by the urethra, vagina and rectum. The muscles are:

1. Levator ani. This can be divided into:
 - a) Ischiococcygeus
 - b) Iliococcygeus
 - c) Pubococcygeus
2. Musculus transversus perinei profundus (part of the urogenital diaphragm).

(Donker, 1976).

The pubococcygeus and transverse perineal muscles are involved in the maintenance of female continence and they are described collectively by Gosling and Dixon (1977) as the "periurethral striated muscle", (P.S. - Figure 1A). This muscle is separated from the urethral striated muscle by a layer of collagen (Donker, 1976; Gosling and Dixon, 1977) and it consists of a mixture of slow and fast twitch cells. It is thought to aid urethral closure during events

which require short-lived increase of urethral resistance, e.g. during coughing, straining etc (Gosling 1979). However, unlike the slow twitch striated urethral muscle the fast twitch pelvic floor striated muscle cannot maintain a sustained contraction.

The pelvic floor may also contract reflexly with increases in intra-abdominal pressure, changes in position and bladder filling (McGuire 1979). In addition it supports and compresses the urethra and its contraction may reflexly inhibit the detrusor motor nucleus (Bradley et al 1974, Brindley et al 1974).

The Pubo-Urethral Ligaments

The pubo-urethral ligaments in the female are often considered to form the main suspensory mechanism of the urethra (Stanton 1977). In one of their first descriptions they were referred to as the "anterior true ligaments of the bladder", (Todd and Bowman, 1856), and later as the pubo-urethral ligaments (of the urogenital diaphragm), (Curtis et al, 1939) and the pubo-prostatic ligaments, (Krantz 1951). A major contribution to our knowledge of this structure was made by Zacharin (1963, 1968 and 1972). In 1963 he described the anterior, posterior and intermediate pubo-urethral ligaments as follows:

The anterior ligament (a continuation of the suspensory ligament to the clitoris arising from the anterior aspect of the symphysis pubis and extending down to the urethra. The posterior ligaments form bilateral

structures consisting of pyramidal-shaped flat bands of tissue with a narrow bony attachment to the postero-inferior aspect of the symphysis and a broader para-urethral insertion near the junction of the proximal and middle thirds of the urethra. An extension of this ligament continues as far as the bladder base. The anterior and posterior ligaments interconnect by means of a relatively tenous intermediate ligament.

Zacharin (1963) examined the histology of the ligaments and his findings were confirmed by Milley and Nichols (1977). The anterior and intermediate ligaments contained striated and smooth muscle and collagen. The posterior ligaments consisted of dense parallel bundles of longitudinally orientated collagen and a substantial amount of elastic tissue. Some smooth muscle was also described but this feature was not included in his later description in 1972. Albers (1973) pointed out that on clinical evidence the ligaments contained a significant muscular element since once they were severed, they immediately retracted. In Cunningham's Textbook of Anatomy (1972) the smooth muscle content of the ligaments in the male is also mentioned but no references are given.

The ligaments are considered to support the upper urethra and indirectly the urethro-vesical junction and to provide a stabilising effect to check the descent of the urethra produced by increased intra-abdominal pressure (Zacharin, 1972). The role of the pubo-urethral ligaments in the aetiology of genuine stress incontinence is

discussed later in this Chapter, (1.2.7).

1.1.2 Innervation of the Female Lower Urinary Tract

The lower urinary tract has autonomic and somatic innervation through the pelvic, hypogastric and pudendal nerves. The profuse motor supply to the detrusor muscle is from parasympathetic preganglionic nerves arising from sacral cord segments 2, 3 and 4; the fibres synapse in the pelvic plexus and the post ganglionic nerves ramify in the muscle bundles of the bladder wall. The presumptive cholinergic innervation of the detrusor muscle cells is indicated by the significant amounts of acetylcholinesterase (an enzyme known to be involved in the degradation of acetylcholine), present in the nerve fibres within the wall of the detrusor. However, the human detrusor has a very poor sympathetic noradrenergic nerve supply (Gosling et al, 1977). This is in contrast to that found in other species, e.g. the cat in which noradrenergic nerves are found in the bladder wall (El Badawi and Schenk, 1968, Caine et al 1975). In humans, therefore, it is likely that sympathetic nerves do not act directly on the detrusor. In this context it has been proposed that sympathetic inhibition of detrusor activity is achieved by noradrenergic nerve terminals acting directly on parasympathetic cell bodies in the pelvic plexus (Gosling, 1979).

Afferent nerve endings are assumed to be in the trigone and bladder neck and their processes travel along either the parasympathetic nerves (for desire to void) to the sacral segments, or the sympathetic nerves

(for pain and distension) to the thoraco-lumbar segments, T11 to L2 (Kura, 1965). The afferents signalling bladder filling are in series with the muscle fibres and are activated by passive stretch and active contraction (Iggo 1955) and by mucosal deformation (Winter 1971).

The bladder neck and urethral smooth muscle are well supplied by parasympathetic nerves which appear morphologically similar to those which supply the detrusor muscle. In contrast to the male (where a profuse sympathetic innervation of the bladder neck is involved in the prevention of retro-grade ejaculation, Gosling, 1979) the noradrenergic nerve supply to the urethral smooth muscle in the female is relatively sparse.

Until recently the striated muscle of the external urethral sphincter and the pelvic floor were thought to be innervated by the pudendal nerve. However, Donker et al (1976) and Gosling and Dixon (1977) have shown that the somatic supply to the external urethral sphincter and the peri-urethral striated muscle is by the pelvic (splanchnic) and pudendal nerves respectively. The clinical significance of these observations is that division of the pudendal nerves will not have a direct effect on the activity of the external urethral striated muscle (Gosling, 1979). Logically, also, physiotherapy for the treatment of genuine stress incontinence should be directed both to the urethral sphincter striated muscle as well as to the striated muscle of the pelvic floor. This is discussed later, (1.4.7).

1.1.3 Mechanism of Continence

Continence is the retention of urine within the bladder until such time as it is socially convenient to void. It depends upon a positive pressure gradient from the urethra to the bladder which must exist at all times except during micturition. Such a gradient may be maintained by contributions from several mechanisms.

Physical Properties of the Bladder

Because the bladder has visco-elastic properties and is approximately spherical it obeys the law of Laplace (Lapides, 1958; Woodburne 1960). This states that the pressure within a vessel varies directly with the tension and inversely with the radius ($P = T/R$). During bladder filling there is an increase in the mural tension as the volume increases but the pressure changes very little (Hinmen and Miller, 1963). In the normal subject, the intravesical pressure rise during filling is less than 15 cm of water. This small change does not affect the pressure gradient between the urethra and bladder.

Urethral Structure

The urethral structures which contribute to its closure pressure are:

Smooth and striated muscle,

Vascular component, i.e. turgor within the

submucosal blood vessels,

Abundant collagenous and elastic tissue,

Oestrogenised mucosal folds of the urothelium.

Smooth Muscle: There is debate concerning the contribution of smooth muscle. Gosling (1979) considers that its oblique and longitudinal orientation would prevent it from contributing significantly to urethral closure. However, Donker et al (1972) suggest that the urethral pressure profile of the dog depends mainly on smooth muscle and Rud et al (1980) found this contribution to be 30 per cent in human females.

Striated Muscle: Also there is no consensus of opinion about the role of striated muscle. Gosling (1979) states that the "slow twitch" fibres of the striated urethral muscles are capable of sustained contraction over long periods and actively contribute to urethral closure. Tanagho et al (1969) concluded that in the dog urethra, the striated muscle is responsible for more than 50 per cent of its maximum pressure and Rud et al (1980) showed that it made up 30 per cent of the intra-urethral pressure in human females. However, Donker et al (1972) found that the striated muscles play a minimal role in maintaining resting urethral pressure.

Vascular Component: Enhorning (1961) first recorded

vascular pulsations in the female urethra and observed that this might contribute to intra-urethral pressure. Berkow and Amboy (1953) and Huisman (1979) described a rich anastomosis between the arterial and venous vessels in the mid-urethra which declines post-menopausally. Raz et al (1972) and Rud et al (1980) found the vascular component amounted to approximately one-third of the closure pressure. However, Donker et al (1972) on the basis of the response to angiotension described a smaller contribution, which Tulloch (1974) also observed.

Collagenous and Elastic Tissue Component: The urethra contains abundant collagenous and elastic tissue which is mixed with muscle fibres within the submucosa (Tanagho, 1975). As mentioned previously, this elastic tissue is thought to contribute albeit passively to urethral closure, (Woodburne 1960). Scarring following surgery or radiotherapy may impede urethral closure and lead to incontinence (Warrell 1969).

Oestrogenised Urothelium: The mucosal lining of the urethra by contributing to "inner urethral softness" has been postulated as being an important component in normal continence (Zinner et al 1978). Since the urethral mucosa would appear to be sensitive to oestrogens (1.5.1), a well oestrogenised urothelium has also been postulated as contributing to the urethral closure mechanism (Caine and Raz 1973) and this is discussed later in this Chapter.

Anatomical Position of the Urethra

At rest, the low intravesical and relatively high urethral pressures, both of which result from the structures already described, maintain continence. It is however necessary for these mechanisms to maintain continence during straining, and coughing, when the intravesical pressure may exceed that of the urethra. During coughing or heavy lifting increases in intra-abdominal pressure are transmitted to the bladder leading to intravesical pressures which may exceed 120 cm of water. As the normal resting maximum urethral pressure is between 70 and 110 cm of water, an intravesical pressure rise following a cough may result in incontinence unless there is another mechanism involved. Thus Enhorning (1961) suggested that the proximal urethra is an intra-abdominal structure to which 80 per cent of intra-abdominal pressure increase is transmitted thereby acting as an additional closing force (James 1976), (Figure 1 B).

A CAUSE OF CONTINENCE AND STABLE DETRUSOR INCONTINENCE
 (After Enhorning, 1961)

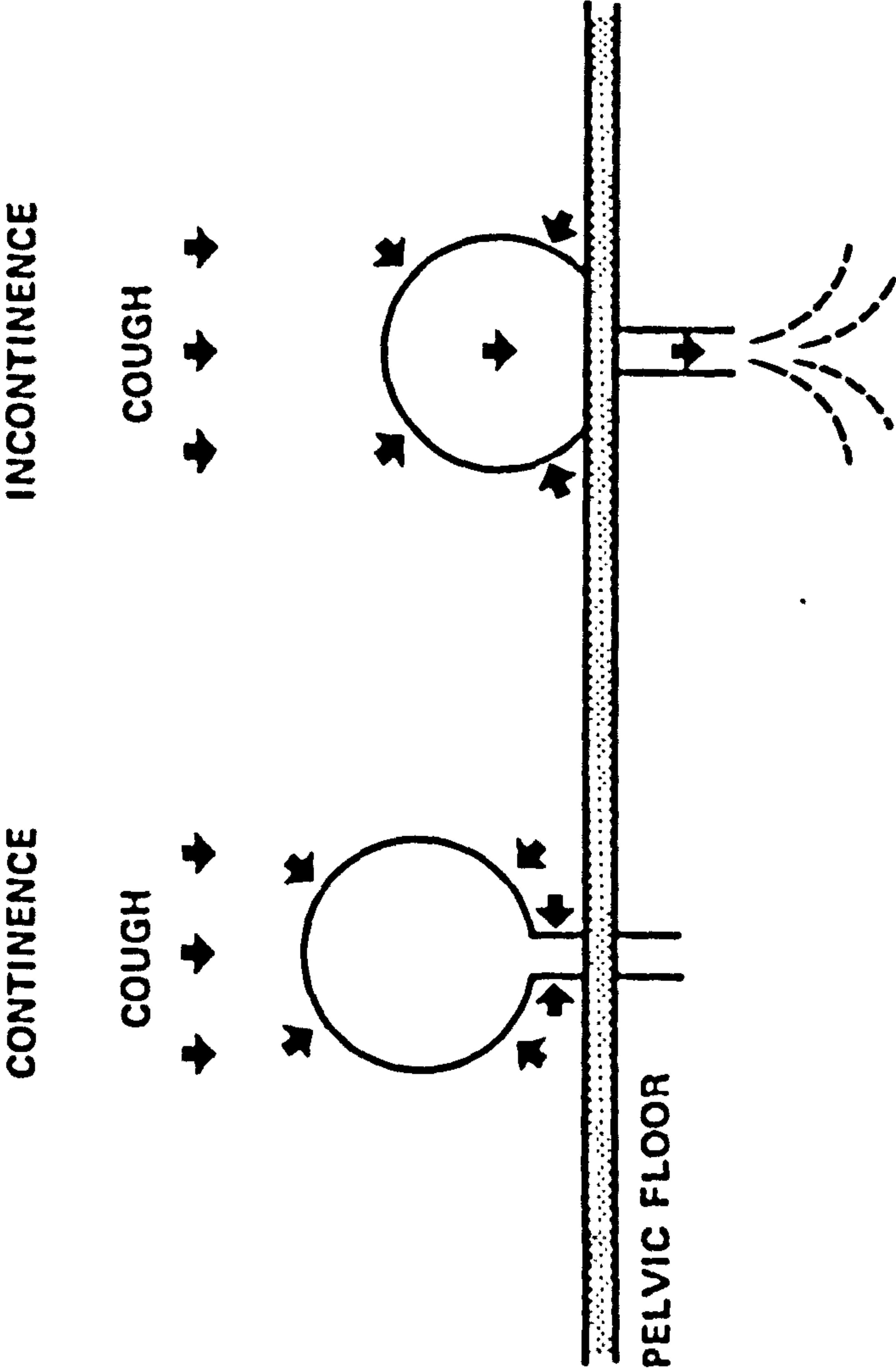


FIGURE 1B

1.1.4 Classification and Incidence of Causes of Female Incontinence

Urinary incontinence is defined as a condition in which involuntary loss of urine is a social or hygienic problem and is objectively demonstrable, (I.C.S. 1976). The causes of female incontinence are outlined below.

Genuine Stress Incontinence

Genuine stress incontinence is the term approved by the International Continence Society (I.C.S.) to describe the condition originally reported by Sir Eardley Holland (Stanton 1977) as "stress incontinence". Other nomenclatures still in use include urethral sphincter dysfunction (Stanton 1977), stress urinary incontinence (Hodgkinson 1970), urinary stress incontinence (Green, 1962) and pressure equalisation incontinence (Beck et al, 1968). Genuine stress incontinence is defined as the involuntary loss of urine when the intravesical pressure exceeds the maximum urethral pressure but in the absence of detrusor activity (I.C.S. 1976). The aetiology of genuine stress incontinence is discussed later however the basic problem is incompetence of the urethral closure mechanism and incontinence occurs on such physical exertions as coughing, laughing, or running.

Genuine stress incontinence is the commonest cause of incontinence in the non-geriatric female patient and its incidence in women attending the Urodynamic Clinic, University Hospital of South Manchester is approximately

55% (Table 1A). This incidence is similar to that found at other highly selected specialist clinics (Moolgaoker et al, 1972, Arnold et al 1973) and may be different from that in the general population.

Detrusor Instability

Detrusor instability is the condition in which involuntary detrusor contractions lead to an increase in intravesical pressure and incontinence occurs when this exceeds the normal (or reduced) intraurethral pressure. Many names are used to describe this condition, namely urge incontinence (Roberts, 1953), uninhibited bladder (Ross, 1956) and the unstable bladder (Bates et al, 1970). In a gynaecological population, detrusor instability is the second commonest cause of incontinence (Table 1A). This condition may be idiopathic or secondary to an upper motor neural lesion, psychosomatic disorder or to cerebral senescence or atherosclerosis in geriatric patients (who have a high incidence of detrusor instability). The objective diagnosis of detrusor instability is made when a detrusor pressure rise greater than 15 cm of water occurs on multiple test cystometry (see 1.3.6).

Genuine Stress Incontinence and Detrusor Instability

Genuine stress incontinence and detrusor instability may co-exist. Its incidence may be difficult to assess because of variations in investigative technique but in the Urodynamic Unit, University Hospital of South Manchester is approximately 10% (Table 1A).

Cause of Incontinence	Number of Patients	Percent
Genuine Stress Incontinence	175	54.8
Detrusor Instability	111	34.8
Detrusor Instability and Genuine Stress Incontinence	30	9.4
Outlet Obstruction	3	0.9
	319	

TABLE 1A

CAUSES AND INCIDENCES OF NON-GERIATRIC FEMALE
INCONTINENCE AT URODYNAMIC CLINIC,
UNIVERSITY HOSPITAL OF SOUTH MANCHESTER, 1976-1979

Overflow Incontinence

Retention of urine in the female is relatively uncommon. Overflow incontinence is defined as involuntary loss of urine when the intravesical pressure exceeds the maximum urethral pressure because of an elevation of intravesical pressure associated with bladder distention but in the absence of detrusor activity (I.C.S., 1976). It is due either to urethral obstruction or detrusor inactivity.

Fistulae

Urogenital fistulae causing incontinence are uncommon in countries where obstetrical services are highly organised, but when they occur they result usually from surgery, malignancy or radiotherapy.

Congenital

Congenital lower urinary tract abnormalities, e.g. ectopic ureter and epispadias are diagnosed usually at or soon after birth, or when the child fails to become dry at the normal age.

1.2 AETIOLOGY OF GENUINE STRESS INCONTINENCE

There is no agreement on the aetiology of genuine stress incontinence. The basic problem is a deficiency of some (or all) of the urethral factors mentioned which maintain continence. In this section, possible contributory aetiological factors are reviewed with particular reference to the role of the posterior pubo-urethral ligaments.

1.2.1 Parity/Pregnancy

Thomas et al (1980) in their general practice survey, found that incontinence was more common in parous women of all ages than in nulliparous, however, it can frequently occur in the latter group also. Nemir and Middleton (1954) and Wolin (1969) studied by questionnaire a series of healthy young nulliparous women and found that just over 50% had the symptom of occasional stress incontinence with 5% (Nemir and Middleton) and 15% (Wolin) suffering from frequent leakage. It is likely that these younger women with stress incontinence have an inherently weaker urethral mechanism which becomes incompetent at times of moderate physical exercise.

In the survey of Thomas et al (1980) there was no difference in the prevalence of incontinence within the parity range of one to three, however, the prevalence was appreciably increased in women who had had 4 or more babies.

It is likely that pregnancy rather than parturition is primarily responsible for the increase incidence of incontinence in parous in comparison to nulliparous women.

Francis (1960) studied the symptoms of stress incontinence in 400 healthy women during and after an uncomplicated pregnancy and found that 118 out of 222 primigravidae (53%) and 150 out of 178 multigravidae (85%) experienced incontinence during a pregnancy. The symptoms started before or during pregnancy but rarely if ever in the immediate puerperium. Also when incontinence was present during or after pregnancy it tended to recur and worsen during and after subsequent pregnancies. Stanton and Wilson (1979) confirmed Francis's findings and suggested that increased progesterone secretion during pregnancy leads to relaxation of the urethral supporting ligaments and smooth muscle which caused incontinence although no evidence was presented for this.

1.2.2 Effect of Progesterone and Oestrogens

Progesterone

Incontinence frequently may worsen in the week preceding menstruation and Stanton (1979) suggests this may be due to the relaxant effect of progesterone on urethral smooth muscle. In the dog Raz et al (1973) have shown that progesterone can produce a decrease in intra-urethral pressure which they attributed to stimulation of urethral beta-adrenergic receptors. Caine and Raz (1973) gave 20 mg. of medroxyprogesterone acetate to humans and observed increased incontinence and reduced intra-urethral pressure.

The urethral pressure profile has been observed to decrease pre-menstrually in 5 continent females (Schrieter et al 1976), however in a larger study of the influence of endogenous hormones on the urethral pressure profile in 27 healthy nulliparous women, van Geelen (1980) did not find any change in the urethral pressures throughout the menstrual cycle. There was also no relationship between serum progesterone and either urethral length or pressure.

Oestrogens

The role of oestrogens in incontinence is not clear and it is discussed later (1.5).

1.2.3 Urethral Length

Lapides (1958) demonstrated in dogs that a minimal critical urethral length was necessary to maintain continence and that incontinence caused by urethral transection was reversed by surgical lengthening. In a later study of 22 patients (Lapides et al 1960), he reported that urethral shortening in the erect position appeared to be the single most reliable diagnostic sign in patients with genuine stress incontinence. However, Hodgkinson (1963) states that this opinion is contrary to clinical experience as incontinence is not consistently produced by amputation of the distal two thirds of the urethra, nor is it relieved by urethral lengthening. Green (1962) reported no change in urethral length in the majority of patients in whom operative repair had been successful in relieving stress incontinence. This has been disputed by Gershon and Diokno (1978) in a small study of 6 patients with increased urethral length following anterior vesicopexy for genuine stress incontinence.

1.2.4 Urethrovesical Pressure and Anatomical Relationships

As stated previously, Enhorning (1961) suggested that the transmission of intra-abdominal pressure to the proximal urethra contributed to the normal continence mechanism. He found using a balloon catheter that in continent women intra-urethral pressure remained higher at rest and during coughing than the intravesical pressure but in genuine stress incontinent patients pressure rises in the bladder overcame those in the urethra. Enhorning suggested this phenomenon could be due to the proximal urethra's position in relation to the pelvic floor musculature (Figure 1B). When the proximal urethra remains above the pelvic floor it shares with the bladder any increased intra-abdominal pressure but if it descends below this level pressure changes are incompletely transmitted to it, thus a reversed pressure gradient would exist so that the pressure in the bladder exceeds that in the urethra and leakage occurs.

Hodgkinson (1953), Tanagho (1974) and McGuire et al (1976) also have emphasised the importance of urethrovesical relationships in the development of genuine stress incontinence. Hodgkinson (1953) using the metallic-bead chain technique showed that in genuine stress incontinent patients, the urethra was highly mobile, and there was marked downward displacement of the urethrovesical junction.

Tanagho (1974) confirmed these findings using cystography and postulated that "loss of support of the urethrovesical junction was the primary problem in genuine stress incontinence". Hypermobility of the proximal urethra with loss of its intra-abdominal position during stress was the commonest abnormality in 80% of 125 incontinent patients studied by McGuire et al (1976).

Jeffcoate and Roberts (1952) on the basis of their extensive studies using cystourethrography in large numbers on both continent and incontinent women concluded that the presence of a normal posterior urethrovesical angle was essential to the continence mechanism and that in genuine stress incontinent patients it was characteristically absent. In Hodgkinson's opinion, (1970), loss of the posterior urethrovesical angle and depression of the urethrovesical junction were synonymous descriptions for the same radiological finding in genuine stress incontinence. The limitations of cystourethrography in the investigation of incontinence are discussed later (1.3.7).

However the concept of the anatomical position of the proximal urethra as an aetiological factor in genuine stress incontinence has been questioned. Some patients with gross descent of the bladder and urethra may not be incontinent (Lapides et al 1960). Kitzmiller et al (1972) found that the same distortion of the urethrovesical angles which has been described in incontinent patients was also present in normal women.

1.2.5 Role of the Posterior Pubo-Urethral Ligaments

The pubo-urethral ligaments, particularly those posteriorly are thought by Krantz (1951) and Zacharin (1972) to support the upper urethra and indirectly the urethro-vesical junction by preventing descent of the urethra during times of increased intra-abdominal pressure. Zacharin (1972) also felt the ligaments were essential for the maintenance of continence and it has been suggested that defects of these structures may predispose to genuine stress incontinence (Krantz 1951; Zacharin 1963, Milley and Nichols 1971, Milley 1979). Zacharin devised an operation for the treatment of genuine stress incontinence in which the posterior ligaments were shortened and strengthened; out of 40 patients he cured and improved 31 and 4 respectively. However their role is not established. Ingelman-Sundberg (1949) and Mulvaney (1951) believed that the posterior pubo-vesical (pubo-urethral) ligaments together with the para-urethral and extra-vesical tissues were responsible for keeping the bladder neck open and producing incontinence, as both reported good results from freeing the urethra and bladder and dividing these ligaments, i.e. vesico-urethrolysis.

The theory that defects in the posterior pubo-urethral ligaments predispose to genuine stress incontinence is examined further in Chapter 2.

1.3 INVESTIGATION OF THE FEMALE LOWER URINARY TRACT

1.3.1 History and Examination

In the past female urinary incontinence has been assessed mainly subjectively by history and clinical examination. Some authors considered that this was sufficient to make an accurate diagnosis in the majority of patients, (Green 1975, Zacharin 1977, Beck 1978), but Hodgkinson (1970) stated that objective assessment was the main guide and that a specially devised questionnaire was helpful. Farrar et al (1975) showed that when the patients symptoms were stress incontinence alone or a combination of frequency, nocturia and urge incontinence the probable diagnoses were genuine stress incontinence and detrusor instability respectively. However, confusion resulted from patients with hypersensitive conditions (cystitis, urethrotrigonitis, interstitial cystitis) who had symptoms similar to detrusor instability. Powell et al (1980) compared the clinical and objective diagnoses of 1,800 patients and showed a poor correlation between the two. The diagnosis was correct in 50% of the patients considered symptomatically to have genuine stress incontinence and in 30% of those thought to have detrusor instability; in those with a history of combined stress and urge incontinence, it was correct in only 14% of cases. Where doubt exists and this will be in the majority of cases, objective assessment is essential, (Brown, 1977).

Clinical examination of incontinent patients is of limited value. Inspection of the genital tract will reveal local pathology, fibrosis of the anterior vaginal wall (with the possible involvement of urethral closure mechanism) or atrophic changes resulting from oestrogen deficiency. Also utero-vaginal prolapse due to pelvic floor laxity will be detected but genuine stress incontinence may occur with or without prolapse and conversely prolapse may or may not be associated with urinary incontinence (Brown, 1977, Cardozo and Stanton, 1980). Demonstrable stress incontinence is a sign which depends on many factors including the severity of genuine stress incontinence and/or detrusor instability, the volume of urine in the bladder, the position of the patient and, to a large extent, the degree of tension in the voluntary component of the urethral closure mechanism, (Brown 1977). In detrusor instability there are no related clinical signs unless it is secondary to a neurological lesion.

In the past two decades there have been significant advances in the investigation of incontinence particularly concerning the objective assessment of the lower urinary tract (urodynamics), which has improved diagnosis and resulted in a more rational approach to treatment. Routine cases of incontinence often require no more than simple methods of investigation whereas complicated cases or recurrent disorders require specialist techniques.

The commonly used investigations will be described and with particular emphasis on those used to evaluate the patients in the various studies to be described later.

1.3.2 Bladder Charts

Bladder charts provide a simple objective assessment of a patients urinary symptoms (Wilson et al 1980). The patient records voiding times and pad or pant changes for 24 hours for 7 days (Figure 1C); the additional record of voided volume adds to the complexity of the chart and is unhelpful in the majority of patients. This record may be used before the patients initial clinic attendance to provide a baseline pattern; thereafter it is completed before and after either conservative or surgical treatment. Figure 1D illustrates its use as a satisfactory method of assessing treatment.

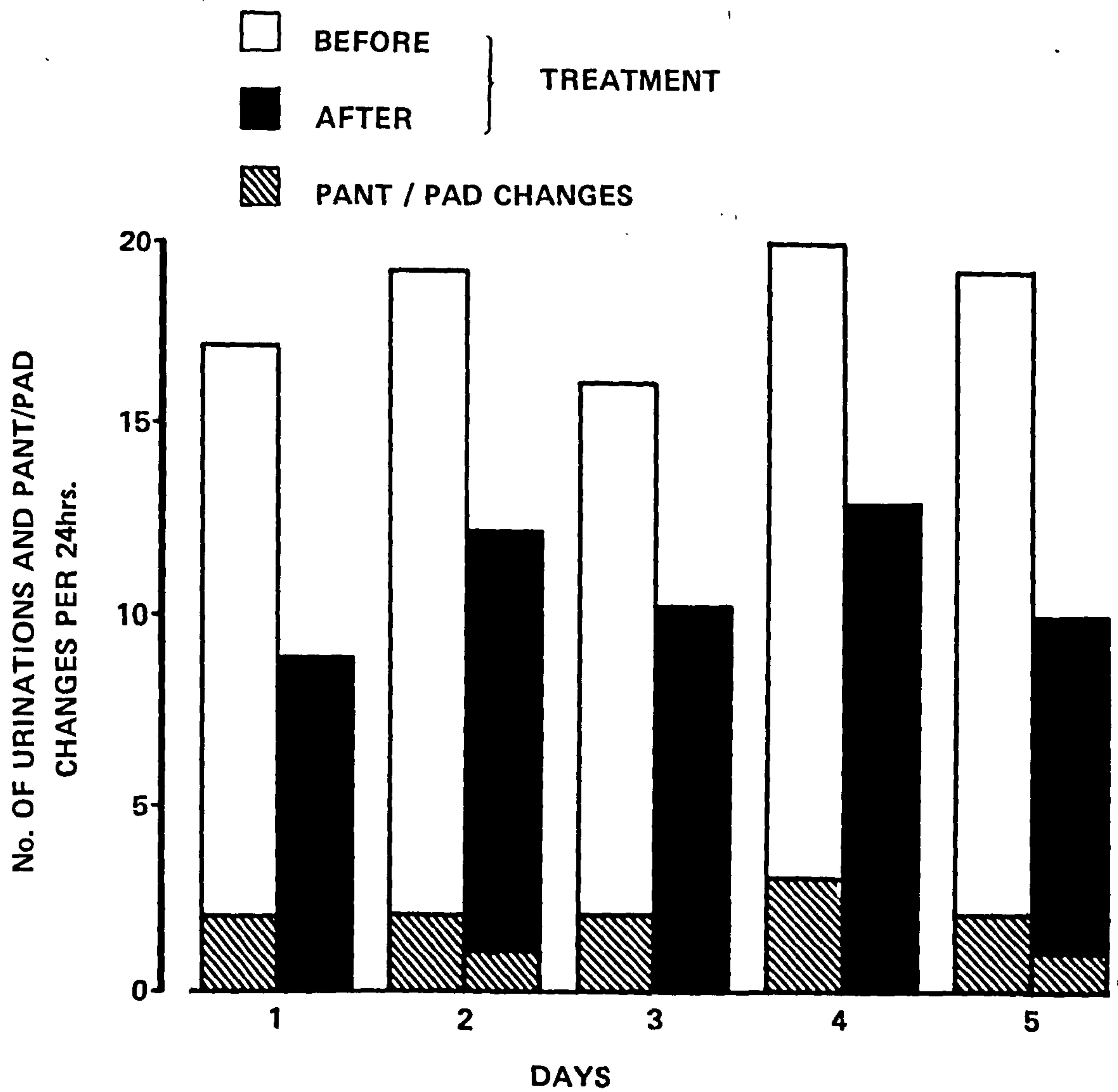


FIGURE 1D - Bladder Chart before and after treatment.

1.3.3 Mid-Stream Specimen of Urine

A mid-stream specimen of urine for culture and sensitivity is recommended in incontinent patients prior to investigation (Stanton 1977). The relationship between infection and incontinence is uncertain; Wolin (1969) noted a significant relationship between stress incontinence and symptoms or a previous history of urinary infection, while Bates (1971) found an unstable detrusor in only 3 of 200 patients with a history of recurrent urinary infection (27 currently affected), urethral syndrome or interstitial cystitis. He also found that when a "sensory" disorder was associated with a stable detrusor, there was increased bladder discomfort on filling cystometry and reduced capacity. Therefore while these conditions do not appear to cause detrusor instability, they may invalidate the results of subsequent investigations.

1.3.4 Uroflowmetry

The measurement of voided urine flowrate is a useful screening test for bladder outlet obstruction although this is a relatively uncommon problem in women. Uroflowmetry is useful also as a preoperative screening procedure in incontinent women as a low peak flow rate prior to surgery may herald retention of urine or voiding difficulties postoperatively, (Stanton et al, 1978).

Various methods of measuring urine flow rate are available. A commonly used flow meter is a modification of that originally described by Von Garrelts (Von Garrelts and Strandell, 1972). This utilises a strain guage weighing transducer which is placed under a cylindrical receptacle into which the patient voids. The rate of increase of weight of fluid is sensed and simultaneously converted to a flow rate. This type of flow meter is cheap and has been shown to be accurate for clinical use and defined experimental situations, (Nyman et al, 1977). The volume voided and flow rate are recorded simultaneously.

A more sophisticated method was developed by DISA Electronic. The urine falls vertically onto a horizontally spinning disc causing drag. This is compensated by feedback control and the urinary flow rate computed from the energy input required to maintain uniform disc speed (Tanmen, 1973). The flow rate is recorded during voiding and the volume afterwards. The

accuracy of this method for clinical use has been demonstrated, (Rowan et al, 1976; Kondo et al, 1977).

Other methods of measuring urinary flow rates are available and include the displacement of air from a closed container (Gierup et al, 1969), the use of Ultrasound (Rollema, 1976) and a "dip-stick" electrode (James, 1977).

In women the normal flow rate is 20 ml per second (Frimodt-Moller and Hald, 1972) but for this to be meaningful a minimal volume of 200 ml of urine must be passed (Rowan et al, 1977). (Figure 1E). A normal flow pattern and rate excludes urethral obstruction unless it has been achieved by an elevated detrusor pressure (Farrar et al, 1976). Equivocal or abnormal levels require cystometry and cystourethrography to assess detrusor response to, and the site of, obstruction.

Accurate uroflowmetry requires certain criteria to be fulfilled. Women may be inhibited by unusual surroundings and therefore void differently from the normal pattern. Therefore they should always be seated to void and given total privacy. Although it is possible to void round catheters, the recorded trace will not be a true measure of the peak flow rate, so, if it is desirable that the bladder pressure is simultaneously measured, uroflowmetry should be performed on another occasion to ensure accuracy of results.

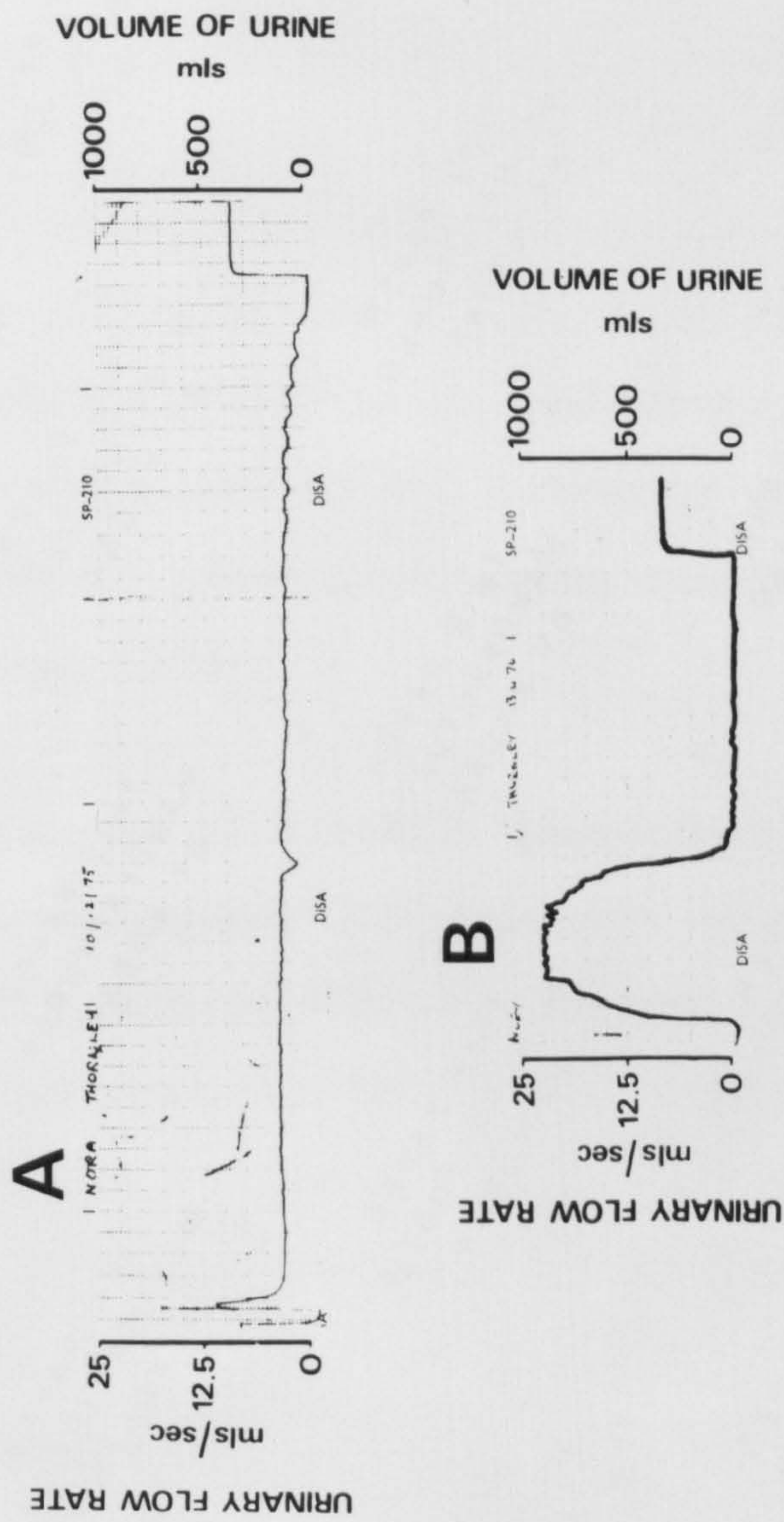


FIGURE 1E - Equivocal voiding flow rate pattern due to an inadequate urine volume (Trace A). Normal flow rate pattern in the same patient with an adequate urine volume (Trace B). (Produced by Permission of A.D.G. Brown and the Editor), Clinics in Obstetrics and Gynaecology).

1.3.5 Endoscopy

Urethroscopy and cystoscopy are simple procedures when using modern fibre optic equipment but the interpretation of the findings requires adequate training. The procedures may be performed under local or general anaesthesia and using either liquid (0.9% saline) or gas (carbon dioxide). In the United Kingdom gas urethrocystoscopy is rarely employed in contrast to the United States, where it is becoming increasingly popular as it enables cystometry, urethral pressure profilometry and endoscopy to be carried out as an "office procedure", using simple apparatus (Robertson, 1978).

Cystoscopy is a useful investigation in patients who complain of urgency and frequency of urination as well as those with voiding difficulties and incontinent patients in whom no cause can be found. The role of cystoscopy in recurrent urinary infections and haematuria falls more within the scope of the urologist. The following information can be obtained from urethrocystoscopy.

Residual Urine Volume

The patient is asked to void immediately before the investigation and the residual urine volume should not exceed 50 mls.

Bladder Capacity

The true bladder capacity can only be assessed under general anaesthesia and should be 400 - 600 mls, thus in patients with detrusor instability when there is frequently a reduced functional bladder capacity it is worthwhile performing urethrocystoscopy under general anaesthetic.

The Mucosa

Inflammatory lesions of the mucosa, papillomata, calculi and neoplasm may cause urgency and frequency. Trabeculation, diverticulae and sacculation may indicate outflow obstruction or neuropathy.

The Ureteric Orifices

These are seen as slits opening at either end of the interureteric ridge. Occasionally, an ectopic ureter orifice can be seen and this is usually below and medial to the real site; this will only cause incontinence if it opens at or distal to the bladder neck.

The Urethra

Inflammation of the urethral mucosa and urethral diverticulae can be diagnosed by urethroscopy; Robertson (1973, 1974) has shown a high incidence of diverticula using a CO₂ system due to greater ballooning and better urethral visualisation (however urethral diverticula are best seen at voiding cystourethrography).

It is important to realise that the appearance of the bladder neck and urethra will give little indication of

their functional ability or disability (Harrison 1978).

1.3.6 Cystometry

Cystometry is the measurement of intravesical pressure changes in relation to volume and is the most accurate method of assessing bladder function. Measurements may be made during both filling and voiding phases. In the female filling cystometry is used principally to measure bladder capacity and to detect detrusor instability which is indicated by the occurrence of detrusor contractions which the patient is unable to inhibit. Voiding cystometry is more important for investigating male patients as it provides objective assessment of obstruction (high pressure and low flow) and evaluation of detrusor contractility.

Mosso and Pellacani (1882) described the first cystometer which consisted of a water manometer to measure the intravesical pressure at different filling volumes which were recorded on a smoked drum. A modification of this method was used by Rose (1927) who introduced cystometry as a clinical test of detrusor function. The main disadvantage of this simple "one-channel" cystometry was that it did not distinguish between the two major components of intravesical pressure - detrusor pressure (created by forces in the bladder wall, ICS 1976) and transmitted intra-abdominal pressure due to straining or coughing.

The advent of pressure transducers allowed accurate measurement of both the intravesical and rectal

(equivalent to intra-abdominal) pressure when used in conjunction with fluid-filled catheters. When the rectal pressure measuring catheter is inserted beyond the anal canal and its distal end is protected from faecal blockage (by a finger stall) it provides a sufficiently accurate representation of intra-abdominal pressure. The rectal pressure measurement can be subtracted electronically from the intravesical pressure to give an accurate measurement of detrusor pressure change. Bates et al (1970) emphasised the clinical value of electronic subtraction of intra-abdominal from intravesical pressure and this technique of cystometry is used widely today but there are many variable factors which require defining (ICS 1976):

1. The Filling Medium

The bladder may be filled with liquid or gas and at present in the United Kingdom the former is used mainly whereas in the United States the latter medium is frequently employed. Water was used with the original cystometers but this has been replaced by 0.9% saline. When cystometry is combined with cystourethrography a radio-opaque contrast medium is required and the cystometric results are the same when compared with those with saline (Arnold et al, 1974).

For gas cystometry, air was the first medium used and Merrill et al (1971) found good correlation in the results between air and water. Unfortunately, one episode of fatal air embolus was reported (Summers et al,

1974) and now carbon dioxide (CO₂) is preferred. The results using CO₂ have been found to correlate well with those of saline (Torrens, 1977) but the compressibility and possibility of very fast bladder filling using gas has been noted to be disadvantageous (Gleason et al, 1976). At filling cystometry Nordling et al (1978) and Walter et al (1979) observed that the first and strong desires to void occurred at lower bladder volumes with CO₂ when compared with water. Also CO₂ has an irritant effect on the bladder mucosa. The advantages of gas cystometry are that it is quick and easy to perform (Bradley et al, 1975) and that the same basic equipment may be used for cystometry, urethral pressure profilometry and endoscopy (Robertson, 1978). However CO₂ does not allow for measurement of flow rate.

2. The Temperature of the Filling Medium

The temperature of the filling medium may be between room and body temperature without affecting the results of cystometry (Stanton, 1977).

3. The route of Filling

Per Urethram (Retrograde): This is the conventional route and although bladder filling and pressure measurements may be made using the same catheter it is more convenient to instill the fluid through a 12 - 14 gauge urethral catheter and to record pressure changes using a 1-2mm fluid-filled catheter. Thus, the filling catheter may be removed when voiding studies are performed leaving the

pressure measuring catheter to record subsequent changes. However the presence of this narrow catheter during voiding has been criticised as it may alter the voiding pattern.

Suprapubic: This is not a popular routine because it is an uncomfortable procedure and there are no real inherent advantages to be gained. There should be at least 250 ml of fluid in the bladder before the suprapubic catheter can be safely introduced. This method has the advantage of not disturbing the urethral mechanism so that voiding is unimpaired. However, the trauma to the bladder may produce its own artefact (Stanton, 1977).

Antegrade: This is the physiological filling of the bladder by urine from the kidneys which may be accelerated by giving a water load and diuretic (Hodgkinson, 1960). It has the advantage that no filling catheter is required and therefore there is less discomfort and interference with the urethral mechanism. The disadvantages are that it is slow, the volume in the bladder is not known and the catheter still has to be inserted into the bladder either suprapubically or per urethram for pressure measurement.

4. The Rate of Filling

In order to perform cystometry in a reasonable length of time, the rate of bladder filling has to be faster than

the physiological rate of 1 ml per minute. In the early days of cystometry incremental filling was performed so that 50 - 100 ml of fluid was added at regular intervals (Lewis, 1939). This did not produce a smooth cystometric curve and nowadays continuous filling at varying rates is used (Bates and Corney, 1971). The rates of filling have been defined by the ICS, (1976) as slow (up to 10 ml per minute), medium (10 - 100 ml per minute) and rapid fill cystometry (over 100 ml per minute). Ramsden et al (1977) compared filling at 100 and 25 ml per minute in 100 patients (61 female and 39 male) and showed that varying the rate of filling failed to provide a significant change in bladder capacity or in the detection of abnormal detrusor contractions.

5. The Posture of the Patient

Cystometry may be performed in the supine, erect or sitting position. The influence of posture change was assessed by Arnold (1974). He stressed the importance of erect (standing) cystometry since 58% of his patients with detrusor instability were not detected by supine filling alone. Ramsden et al (1977) however found that supine filling detected approximately 90% of cases of detrusor instability. However the patient population and technique of erect cystometry were different (approximately 40% of their patients were males and erect filling was conducted in the sitting position).

In the diagnosis of genuine stress incontinence the object is to identify urethral incompetence in the absence of abnormal detrusor activity (instability) which is usually excluded by cystometry. The technique of cystometry used in the pubo-urethral and conservative treatment studies is described later (3.2) along with the "provocative tests" used to detect and exclude detrusor instability. A retrospective study (Chapter 4) was carried out to assess the value of these tests in provoking detrusor instability and to evaluate postural cystometry and the effect of age.

However, cystometry is an invasive and non-physiological procedure and a strong argument against its use is the lack of published data on this test in large series of normal women, though normal values are available from studies of 19 young females (Zinner and Pacquin, 1963) and 15 women aged over 40 (Walter et al 1979). Although the relationship of detrusor instability to outcome of treatment has been assessed (Arnold et al 1973, Stanton et al 1976) the interpretation and significance of cystometric observations are difficult to establish in the absence of normal values from large numbers of women.

1.3.7 Cystourethrography

Cystourethrography has been used for investigation of female incontinence since the early 1950's. Jeffcoate and Roberts (1952) showed that there was an association of genuine stress incontinence with loss of the posterior urethrovesical angle, funnelling of the urethrovesical junction at rest and an increased downward movement of the bladder base with rotation of the urethra on straining and during micturition. Hodgkinson (1953) using the metallic bead-chain technique demonstrated descent of the urethrovesical junction and bladder base on straining in genuine stress incontinence. Green (1968) pointed out that an abnormal urethral axis (angle of inclination between the proximal urethra and the bladder base) was also associated with genuine stress incontinence and he used this to decide the type of incontinence surgery. The importance of the location of the urethrovesical junction in genuine stress incontinence was emphasised by Tanagho (1974).

However, measurement of the posterior urethrovesical angle and other anatomical changes on static radiographs have limitations in the investigation of incontinence. Loss of the posterior urethrovesical angle is thought simply to be a reflection of an open proximal urethra which may be due to either genuine stress incontinence, detrusor instability or a combination of both (Bates, 1971, Harrison 1978) and simultaneous pressure measurements are needed to distinguish accurately between these. Even when this sign is present it may not be

significant as at rest, some incontinent patients have a closed proximal urethra with a normal urethrovesical angle and some continent women have an abnormal angle (Kitzmilller et al, 1972, Stanton 1977).

1.3.8 Synchronous Video Pressure Flow Cystourethrography

A significant advance in lower urinary tract investigation came when Enhorning et al (1964) described simultaneous cystometry and radiological screening of the bladder and urethra both of which were recorded by individual television cameras, the images being fused to give a comprehensive picture of bladder and urethral activity and anatomical changes. The final image was photographed using a cine camera so that a permanent record was obtained. Enhorning et al did not employ intra-abdominal pressure measurements initially but this was added later so that detrusor activity could be obtained. This investigation was performed with the patient seated on a commode over a flow meter and radiographic screening was postero-anterior. This did not give a good view of the bladder neck and was later altered to oblique radiological screening.

Enhornings technique was adapted for routine clinical use by Bates et al (1970) and described in detail by Bates and Corney (1971). The method of performing "Synchronous cine pressure flow cystourethrography" is now a routine technique of urodynamic assessment in many specialist units. The comprehensive information obtained by this investigation in female incontinent patients was assessed by Arnold et al (1974). Genuine stress incontinence is diagnosed (in the absence of a detrusor contraction) by an open proximal urethra either at rest or on coughing without leakage of urine (Grade 1) or

with leakage (Grade 2) (Whiteside, 1973).

1.3.9 Urethral Pressure Profilometry

The urethral pressure profile is a graphic record of the pressure recorded along the length of the urethra. It is generally regarded as a urodynamic investigation but since it is performed usually when the detrusor and urethra are at rest it is primarily therefore a static investigation.

The perfusion method of measurement was first described by Brown and Wickham (1969), improved by Harrison and Constable (1970) and assessed by Edwards and Malvern (1974) and Abrams et al (1978). A small 7-12 Charriere gauge urethral catheter with side holes near the distal end is infused with water at a rate of 2 ml per minute. As the catheter is slowly withdrawn from the bladder along the urethra, the pressure resisting the constant outflow of water is monitored by a standard transducer and recorded.

The International Continence Society established a Standardisation Committee (1976) which recommended that a common terminology be adopted in published accounts of profilometry. The recommended nomenclature is shown in Figure 1F. The curve shown may be taken as a diagrammatic representation of a profile from a female patient. The maximum urethral pressure usually occurs at about the mid-third of the urethra - the urethral segment where the striated muscle is at its maximum condensation (Tanagho, 1978; Gosling, 1979).

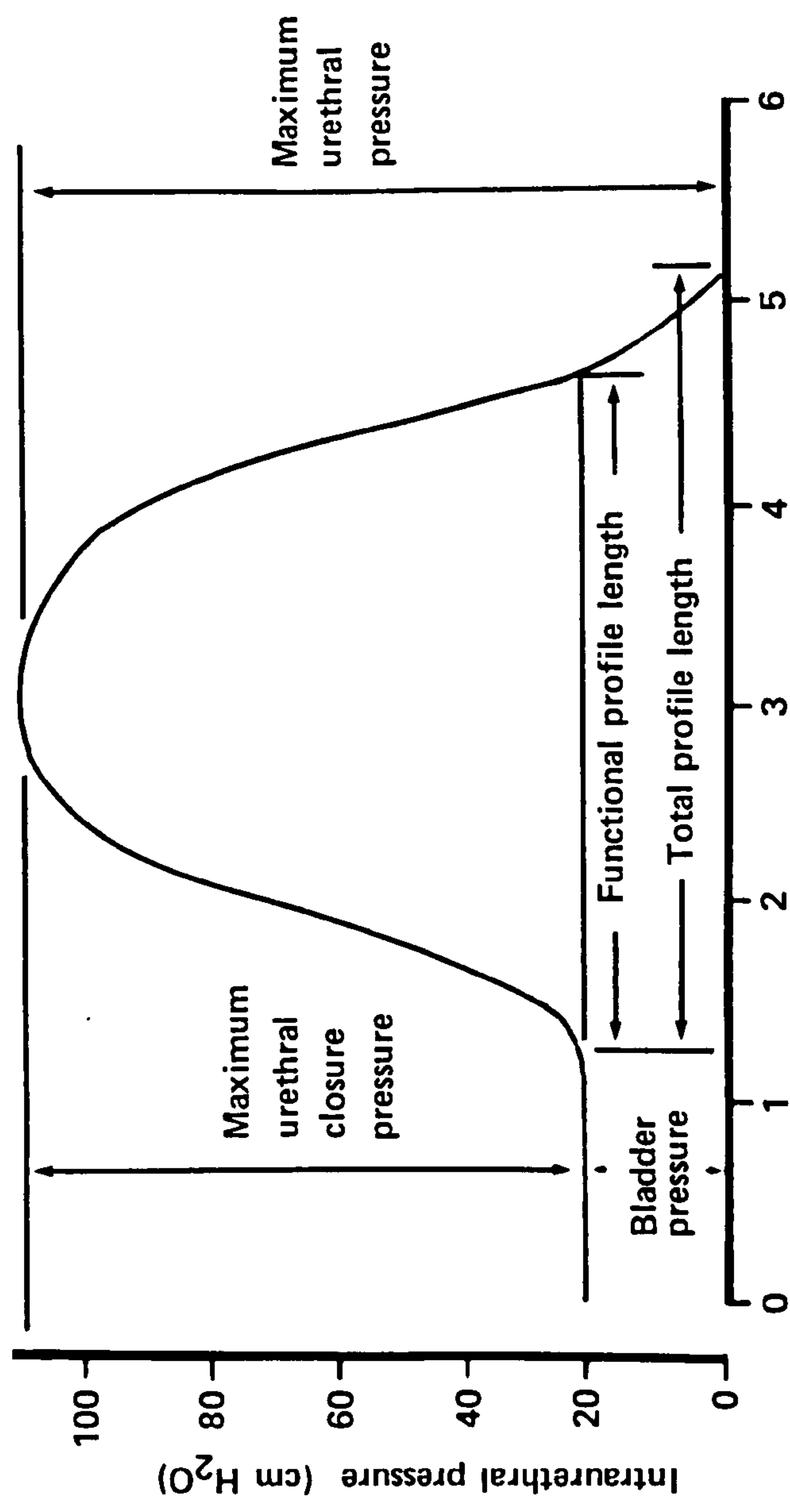


FIGURE 1F - Schematic representation of Urethral Closure Pressure Profile.

The most significant error in measurement of urethral pressure by the Brown and Wickham method is caused by the slow response of the system to increasing pressure (Abrams et al, 1978). However, provided the perfusion rate is between 2 and 20 mls per minute, and the catheter withdrawn at less than 20 cm per minute, satisfactory measurements may be obtained, (Edwards and Malvern, 1974). It has been found to be a reproducible test when repeated in the same patients at the same examination and there was no significant difference between estimations carried out at varying time intervals the maximum of which was 6 months (Edwards and Malvern, 1974; Meyhoff et al, 1978).

The urethral pressure profile was used in the studies described later as a means of evaluating physiotherapy and oestrogen treatment in genuine stress incontinence. Generally, it is thought to be more important as a research rather than a clinical investigation. Although women with genuine stress incontinence as a group have been shown to have lower peak resting pressures than continent women, there is a wide scatter of values so that a single profile measurement is unlikely to be of diagnostic significance (Harrison, 1978).

Other methods available of measuring the urethral pressure profile include fluid-filled balloon-ended catheters (Enhorning et al, 1964; Tanagho et al, 1969), membrane catheters which utilise pressure transmission across a single or double latex membrane (Tanagho and Jonas, 1977) and microtransducer-tipped catheters

(Ulmsten and Asmussen, 1975). These have the advantage of avoiding the inaccuracies of fluid-filled systems such as delayed time response and air bubbles, but as the transducer faces in one direction it may not give a completely accurate picture of occlusive forces. They are also expensive and fragile.

1.3.10 The Fluid Bridge Test

In the diagnosis of genuine stress incontinence the object is to identify those cases in which fluid passes or could pass into the urethra when there is raised intra-abdominal (hence intra-vesical) pressure and in the absence of detrusor contractions. Cystourethrography (without pressure measurements) relies on changes in the appearance of the proximal urethra (anatomical position or fluid entry) or leakage can be visualised. Other methods seek to identify these cases by inference from pressure relationships between the bladder and urethra (Enhorning, 1961, Shelley and Warrell, 1965). If urethral pressure falls below bladder pressure during stress, it is inferred that urine leakage must occur. The interpretation of the results relies on theories of pressure transmission from the abdomen (Green, 1968) but the tests cannot prove that the proximal urethral opens during stress. If the urethra opens transmitted hydrostatic pressure from the bladder will also reach the test point causing confusion in the interpretation of the urethral pressure recording, (Sutherst and Brown 1980).

Urethral pressure profile measurement by the water infusion method of Brown and Wickham (1969) is not suitable usually for "stress testing" because the response time for the apparatus is too slow. However, this deficiency has been turned to advantage in differentiating between urethral wall pressure and hydrostatic pressure transmitted from the bladder in the Fluid Bridge Test (FBT) (Brown and Sutherst, 1978); the

principle is that in genuine stress incontinence when the bladder neck opens a "fluid bridge" is established between bladder and proximal urethra and pressure changes become equal momentarily (Figure 1G). If the proximal urethra remains closed during the cough, the urethral pressure recording will fall short of the bladder pressure because the measuring system (with reduced flow rate) cannot respond to the rapid changes in wall pressure (Figure 1H).

In a clinical evaluation of the FBT (in supine position) Sutherst and Brown (1980a) compared 23 normal continent women with 67 stable detrusor incontinent patients. 39 of the 67 incontinent women had a positive FBT compared with only one of the women of the control group. However 8 of the 28 patients with a negative FBT had a "false negative" result as they had demonstrable stress incontinence on clinical examination. In a later review Sutherst and Brown (1980b) (which also included erect testing), the FBT was predominantly positive (70%) in the incontinent subjects and negative (92%) in the controls.

The Fluid Bridge Test was one of the methods used to diagnose genuine stress incontinence in the studies of conservative treatment described later. A comparison of this test with the other commonly used method to diagnose genuine stress incontinence, cystourethrography is presented in Chapter 4.

FBT POSITIVE

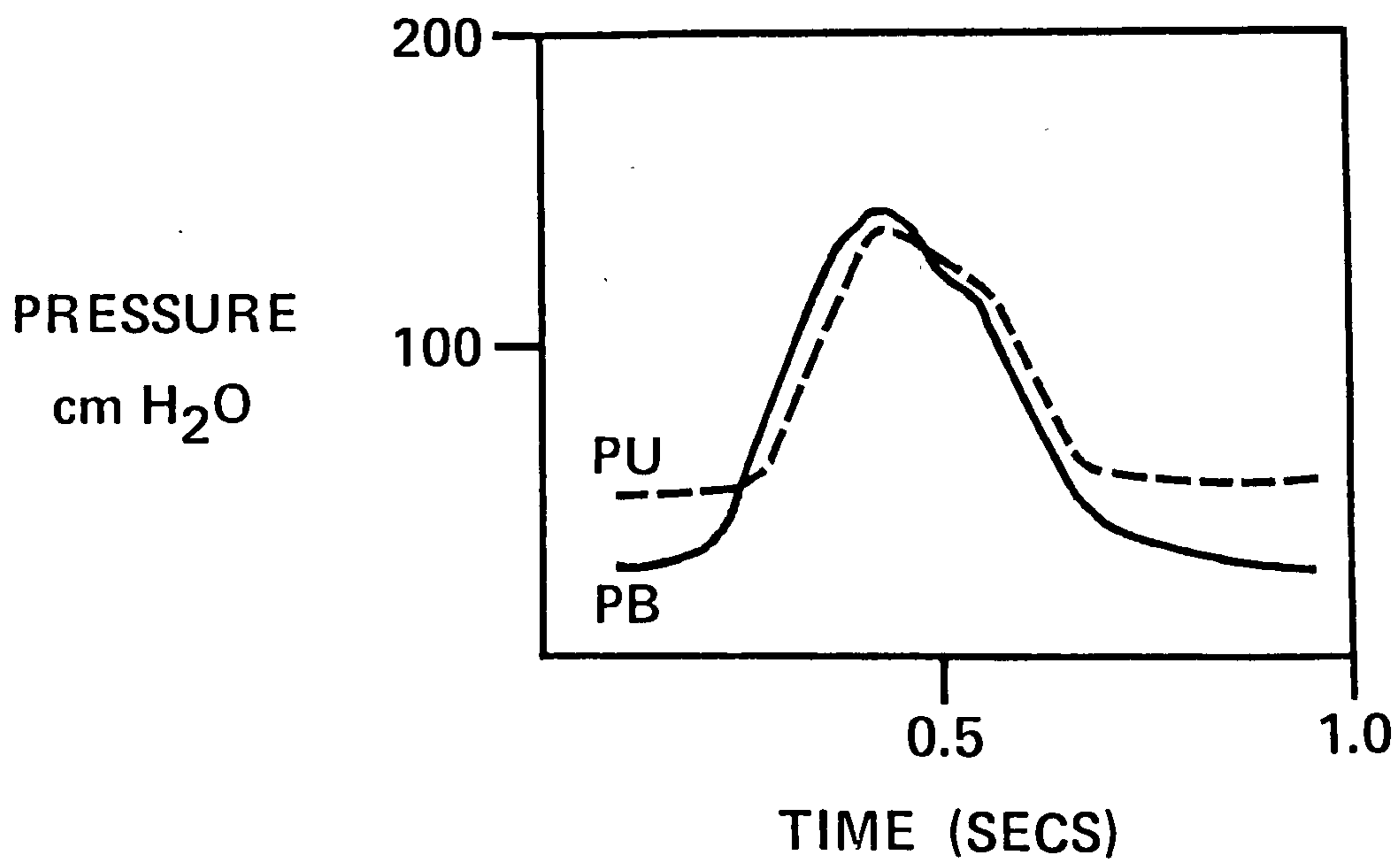


FIGURE 1G - Bladder neck opens momentarily during cough.
 Urethral pressure derived from bladder (i.e. a Fluid Bridge has occurred).
 (PU = Urethral Pressure; PB = Bladder Pressure).

FBT NEGATIVE

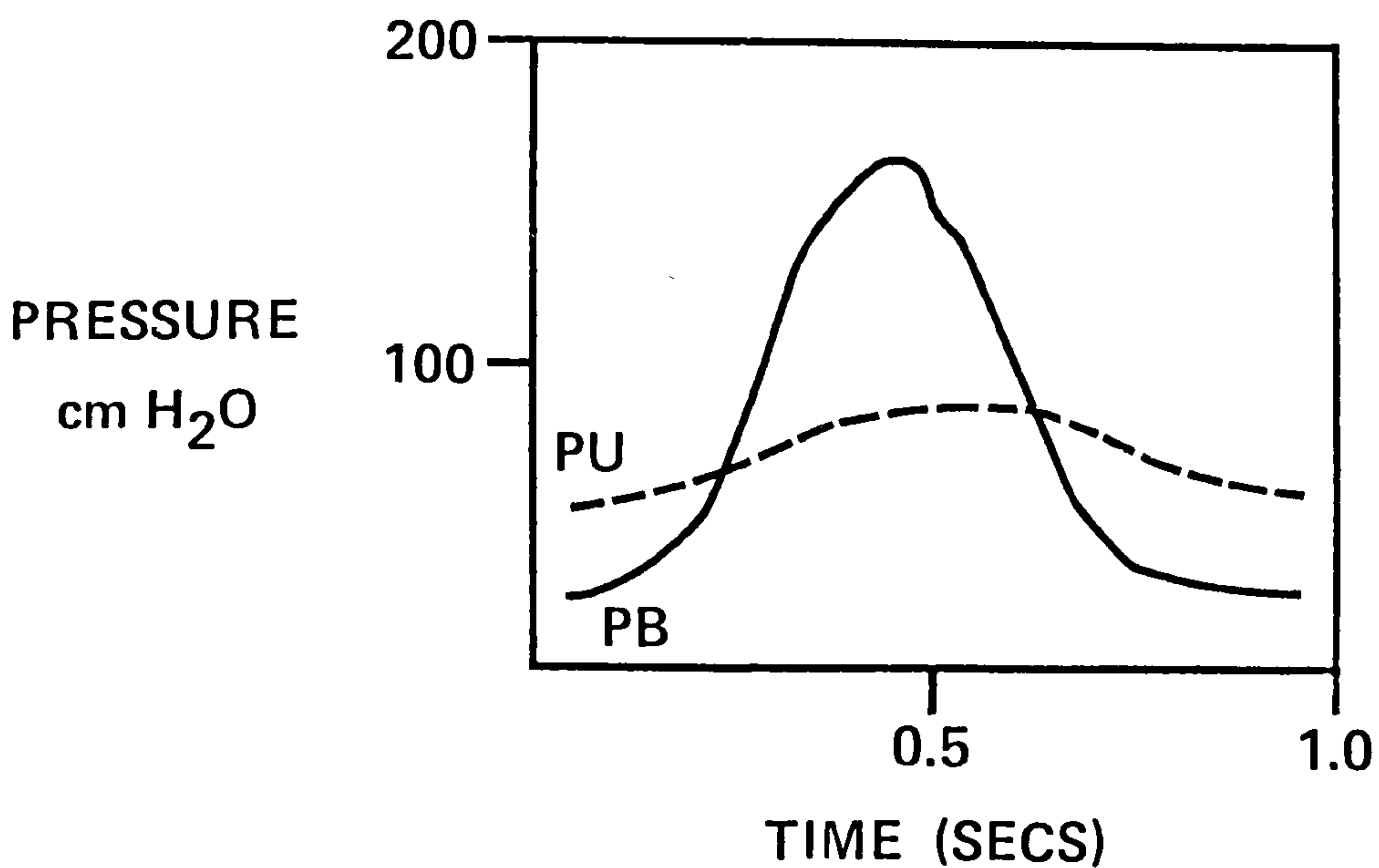


FIGURE 1H - Bladder neck remains closed during cough.
 Urethral pressure derived from wall.

1.3.11 Quantitative Assessment of Urine Loss with Particular Reference to the Uriilos System

An accurate quantitative assessment of urinary incontinence is required to assess the degree of leakage and the effect of treatment. Simple techniques include bladder charts, wearing protective pads which are either weighed or, after prescribing phenazopyridine hydrochloride (Pyridium) to colour urine orange, inspected. Complicated investigations, for example, synchronous cystometry and cystourethrography, may demonstrate leakage (Brown, 1977). However, none of these tests measure incontinence accurately.

The Uriilos System was designed to quantify urine loss by an incontinent patient (James, 1971, James and Flack 1974, Caldwell, 1974); it consists of a disposable nappy on one side of which are attached electrode strips containing dry electrolyte. In the presence of urine the electrical capacitance between electrodes changes and this may be measured when connected to a meter which will record up to 100 ml of urine (Figure 1I).

Rowan et al (1976) and Stanton and Ritchie (1977) described technical and clinical evaluations. They observed that using a measured quantity of urine the difference between two nappies was 13 per cent (Stanton and Ritchie) and between two packs of nappies was 17 per cent (Rowan et al).

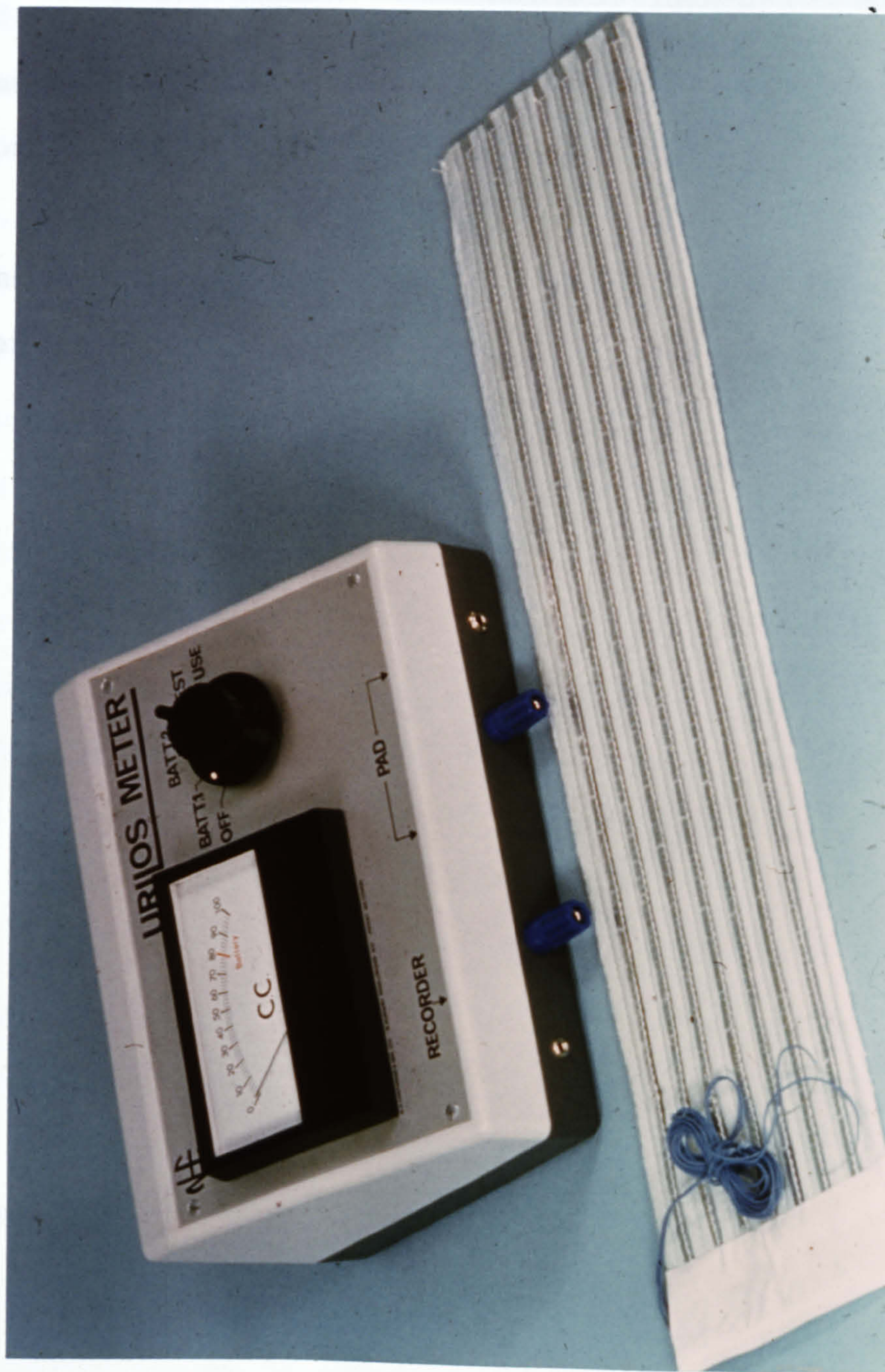


FIGURE 1I - URILOS NAPPY AND METER

Their clinical assessment consisted of the patient attending with a comfortably-full bladder and wearing a nappy which was attached to the meter by a variable length of lead. Several manoeuvres were performed to reproduce the conditions causing incontinence. However, this method has the disadvantage of the artificial hospital environment and the limitations imposed by the length of lead. The method used in the studies of conservative treatment is described later (3.5) and it is evaluated in Chapter 5.

1.4 CONSERVATIVE TREATMENT OF GENUINE STRESS

INCONTINENCE: THE VALUE OF PHYSIOTHERAPY

Incontinence is a common female problem (Nemir and Middleton 1954; Wolin 1969), but treatment should be considered only when it is troublesome and this depends on its frequency and severity as well as the patient's response to leakage (Brown 1977). It is generally accepted that the best treatment of severe genuine stress incontinence is surgical and that the results of suprapubic procedures are superior to vaginal operations (Hodgkinson 1970; Stanton 1979). However the treatment of mild to moderate incontinence is less certain but conservative measures should be tried initially as frequently they are helpful (Brown 1977). Also there are some patients for whom surgery is inappropriate, for example those who are unwilling or not medically fit for surgery and those women who wish further pregnancies as later vaginal deliveries may adversely affect successful surgery (Stanton 1979). There is therefore a need for conservative treatment of genuine stress incontinence and there follows a review of the measures available with particular emphasis on physiotherapy.

1.4.1 Diet

Correction of obesity may improve incontinence presumably by reducing intra-abdominal pressure (Stanton 1977). There is a general tendency for incontinence surgery to be performed irrespective of patient weight.

Strict attention to diet has the advantage of transferring part of the responsibility for treatment to the patient herself and even if incontinence is unchanged, surgery when necessary will be made easier technically and such post operative complications as wound-infection and deep venous thrombosis will be less likely.

1.4.2 Associated Medical Conditions and Fluid Restriction

Chronic bronchitis with its associated cough will aggravate incontinence and therefore rigorous treatment, including forbidding smoking, is essential. Enquiry should be made of patients average fluid intake, which in incontinent patients is usually reduced. If not, advice to restrict it will reduce incontinence. Also, the current liberal use of diuretics will tend to aggravate incontinence.

1.4.3 Drug Treatment

On theoretical grounds, drugs which raise the intra-urethral pressure would be of value in genuine stress incontinence. Pharmacological studies (Nergardh and Boreus 1972, Raz and Caine 1972) have shown the presence of both α and β adrenergic receptors in the human, cat and dog urethra and alpha adrenergic stimulating agents have been used in the treatment of genuine stress incontinence. 8 out of 13 females became completely dry using phenylpropanolamine and there was a significant increase in the urethral pressure profile (Awad et al 1978). Stewart et al (1976) found 23% of 77 women to be cured on this therapy and Montague and Stewart (1979) confirmed the effect of phenylpropanolamine on the urethral pressure profile which was more pronounced in patients with genuine stress incontinence than control women.

However these results are surprising in view of the anatomical studies of Gosling et al (1977) which showed that the noradrenergic nerve supply to the female urethra smooth muscle was relatively sparse (1.1.2). A possible explanation could be that smooth muscle receptors are involved which are not normally innervated by noradrenergic nerves (Gosling et al 1977).

The long term use of sympathomimetic drugs in the treatment of genuine stress incontinence may not be as practical as physiotherapy and surgery and at the present moment they only have a small place in management.

1.4.4 Mechanical and Electrical Devices

The underlying principle of most mechanical and electrical devices is to increase the pressure within the urethra over that of the bladder thereby producing a positive urethral closure pressure. The mechanical aids are thought to act by compressing the urethra and elevating the urethrovesical junction, whereas the electrical devices attempt to produce a sustained contraction of the urethral and peri-urethral striated muscle and thus increasing the intra-urethral pressure.

Mechanical Devices

The Habib device is C shaped and carved out of a solid piece of silicone plastic to fit each patient. One limb is placed inside the vagina and compresses the anterior vaginal wall whilst the other limb rests externally on the pubis. The device may be self retaining but in most patients it is held in position with waist straps and perineal bands. Habib (1969) described a series of 15 patients who had worn the device without problems for 5 months and had achieved continence. However the device is not generally available.

The Edwards pubo-vaginal spring consists of 3 parts (Figure 1 J). The first is a fenestrated triangularly shaped pressure pad which fits anterior to the symphysis pubis. This is connected by a spring arm to a corrugated plastic pressure pad which is placed intra-vaginally and exerts pressure on the anterior vaginal wall and urethra.

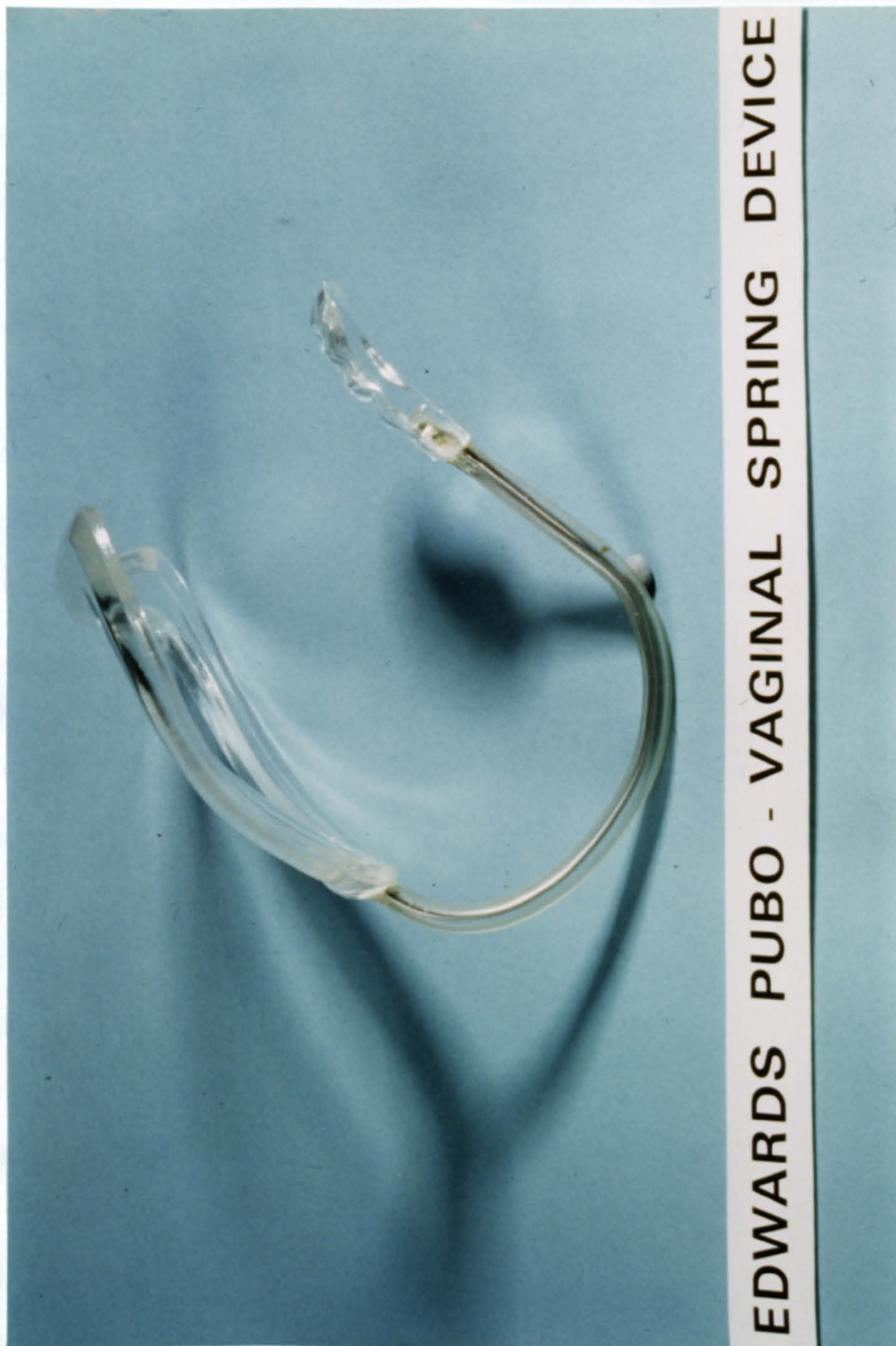
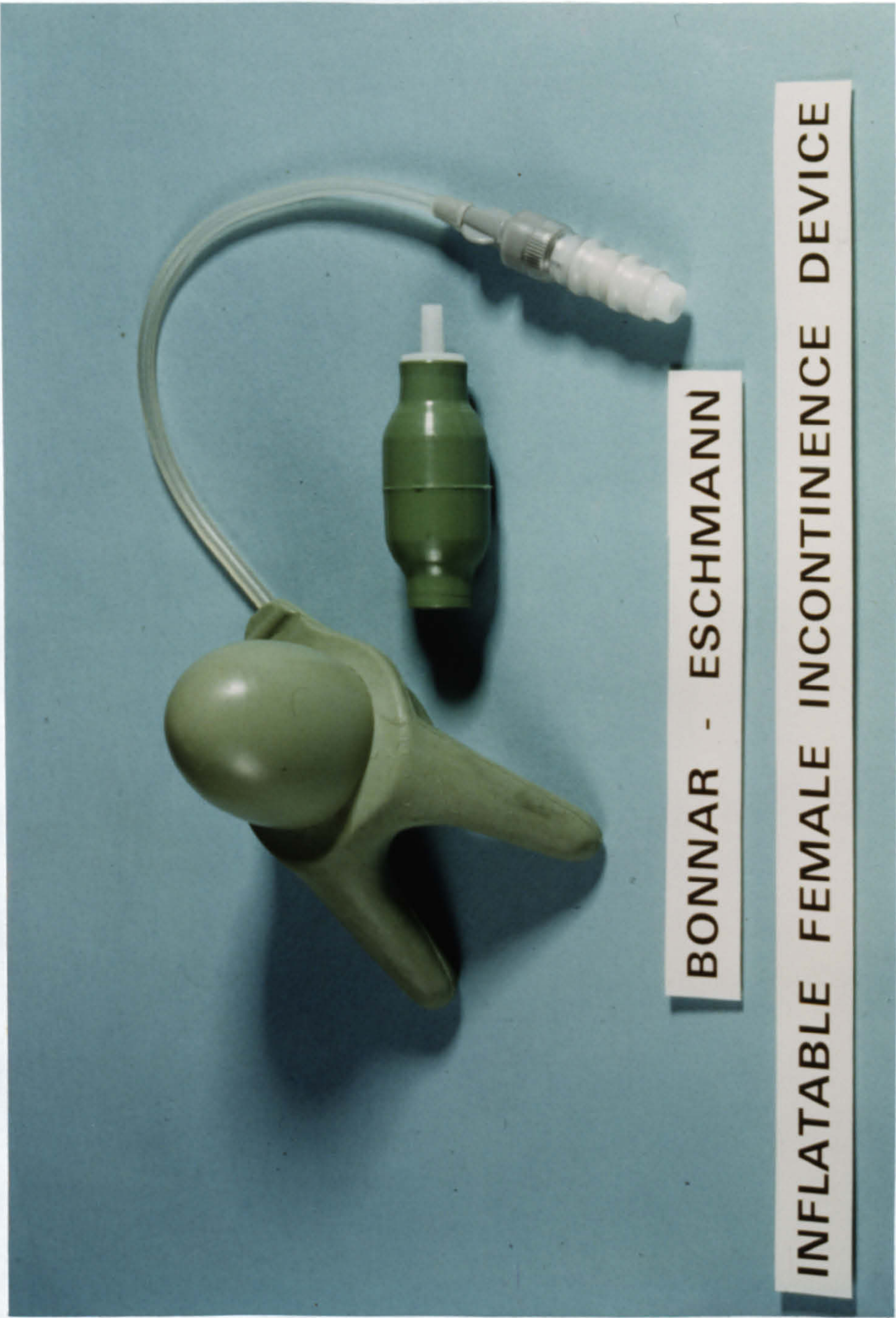


FIGURE 1J

Edwards and Malvern (1973) found a 70% improvement in 36 genuine stress incontinent patients who had been treated with this device and followed up for between 5 months and 4 years.

Bonnars device is made of soft latex with an inflatable balloon on its upper surface (Figure 1 k). When inflated (with between 20 and 40 ccs of air) it elevates the urethrovesical junction and the proximal urethra. Cardozo and Stanton (1978) evaluated this device and found a subjective improvement in approximately half of the 20 patients tested; they noted also an increase in urethral pressure profiles and elevation of the bladder neck.

The disadvantages of these aids include discomfort, displacement and the possible need for removal before micturition; also elderly patients may not have the manual dexterity required to manipulate them. In his review Edwards (1975) concluded that mechanical devices were indicated in patients awaiting incontinence surgery or those who refuse, or are unfit for operation. None of these devices should be used in patients with a residual urine volume of greater than 100 ml, in cases where there is vesico-ureteric reflux and where vaginal sensation is impaired (Edwards 1975; Stanton 1977).



BONNAR - ESCHMANN

INFLATABLE FEMALE INCONTINENCE DEVICE

FIGURE 1K

Electrical Devices

These comprise anal plugs, vaginal pessaries and implanted electrodes. Up to 50 percent of incontinent patients have been improved by an anal plug (Hopkinson, 1972), however its disadvantages are that it is aesthetically unacceptable to some patients, it needs to be removed before defaecation and passage of flatus, and may be impossible to use in the presence of haemorrhoids or an anal fissure. Vaginal pessaries come in different shapes; ring, Hodge pessary and Vitalograph Continator which is cylindrical with a narrow middle for better retention. The latter device has been found to be the most successful producing an improvement in 53% of patients (16 out of 30), the majority of whom had genuine stress incontinence (Doyle et al 1974). For long term use electrodes have been implanted surgically and the stimulus transmitted from an external generator unit using a radio frequency transmission. The implanted electrodes are sutured to the anterior fibres of levator ani (one on either side of the bladder neck) after being positioned to produce a maximum rise in intra-urethral pressure or a visible contraction of the levator ani muscle (Glen 1975, Stanton 1977). De Backer (1973) reviewed by questionnaire the results from 16 centres of 354 implants for mixed incontinence conditions; 64% of the patients were said to be improved. However, implants are no longer popular for the treatment of genuine stress incontinence because of frequent mechanical faults, morbidity due to infection and because superior results are obtained by other methods (Stanton 1977).

The value of electrical devices was assessed by Edwards and Malvern (1972) who concluded that the indications for use were similar to those for surgery and that they were useful only for short term treatment. In a later review however, Glen (1975) considered them a valuable addition to treatment.

1.4.5 Protective Clothing and Collection Devices

In some patients incontinence cannot be controlled completely and protective clothing is required to ease discomfort and help them lead a reasonably normal life. Various pads, pants and collection devices are available.

Incontinence Pads and Pants

The basic principles are to separate the patient from her leaked urine and to reduce to a minimum odour which may be offensive to others as well as to the patient herself (Willington, 1976). Marsupial "Kanga" pants (Willington et al 1972) were devised to meet these criteria. These pants consist of hydrophobic material which attracts urine through it onto an absorbant pad within an exterior waterproof pouch; the patient remains dry and with a large capacity (250 - 500 ml {doublet pad}) frequent changes should be unnecessary. Gel pads also may be used. These are cellulose-impregnated pads which convert the urine into a colloid and the offensive smell of decomposing urine in contact with air is thereby abolished. There are several other types of pants and pads available (e.g. Mölnlycke) and the ideal management is to have a nurse trained in the use of the whole range of incontinence aids so that individual needs of the patient are catered for.

Collection Devices

Urinals and bed pans designed for women are available and these have been reviewed and found to be useful in some

intractable cases by Mandelstam, (1977) .

1.4.6 Indwelling Catheterisation

This technique may be necessary for patients with neuropathic bladders, elderly bedridden or chair-bound women and as an alternative in those whose symptoms are severe enough to warrant diversion (Stanton 1977).

Catheters however also have complications and they must be properly looked after if they are not to become more troublesome than the original incontinence (Willington, 1976). Their disadvantages include urethritis (although the modern Silastic, latex or neoplex catheters are less irritant than the old rubber catheters) and leakage around the catheter especially in detrusor instability. Urinary infection is another complication but this may be minimised by an aseptic technique of catheterisation, a closed drainage system, bladder irrigation and administration of chemotherapy or antibiotics (Stanton, 1977).

1.4.7 Physiotherapy

The use of physiotherapy in urinary incontinence has never been assessed objectively. As mentioned previously (1.1.1) continence is influenced by the activity of the striated musculature of the urethra and the pelvic floor. Hence on theoretical grounds, physiotherapy to increase the effectiveness of these striated muscles would be of benefit in genuine stress incontinence. In the past various forms of physiotherapy have been used:

Pelvic Floor Exercises

Kegel (1948) described the use of pelvic floor exercises for incontinence and he devised a "Perineometer" (1949), to enable the patients to be aware of the muscles to contract. It consisted of a vaginal rubber chamber attached by a tube to a manometer which recorded the pressure achieved by pelvic floor muscle contractions. Kegel's earlier studies (1951) recorded an 84% cure rate and similar results have been noted by Jones (1963). In these studies while there was an objective assessment of pelvic floor contractility using the perineometer, there was little or no objective assessment of the type or degree of incontinence nor of the treatment results.

Faradism

Faradism (muscle stimulation by low frequency current) has been used for years as an adjunct to pelvic floor exercises and it is claimed to re-educate the patients awareness of muscle contractility (Mandelstam 1978) and to

improve muscle "tone" (Moore and Schofield 1967). It has been described both with general anaesthesia (Moore and Schofield 1967, Glen et al 1976) and without (Mandelstam 1978). The use of a general anaesthetic appears to be unjustified (Scott et al 1969); using a togometer (a balloon introduced into the rectum to measure pelvic floor contractility) they showed that at each current value the pressure recorded was less when the subject was anaesthetised than when conscious. The results of faradic treatment are conflicting. Moore and Schofield (1967) using maximum perineal stimulation under general anaesthesia found that 10 out of 18 patients were either considerably or completely relieved of their symptoms of stress incontinence. Schach (1972) using a similar technique recorded an improvement in 27 out of 30 patients which lasted for 3 months. However Glen et al (1976) did not find any improvement in their series of 19 incontinent patients. Although Glen et al used urethral pressure profiles in their patient selection for treatment, on the whole these faradic studies had similar limitations to those of pelvic floor exercises suffering from lack of objective assessment.

Mandelstam (1978) felt that the value of faradism was to re-educate the patients awareness of pelvic contractility but the muscle was strengthened only by exercise. Scott et al (1969) compared 6 methods of faradism by measuring rectal pressure response via a togometer described previously. They found that the most effective results of levator ani contraction were obtained by a metal rectal electrode with a large indifferent electrode

over the sacral area. However, no clinical results were given. Most patients also find the rectal electrode aesthetically unsatisfactory, and as Mandelstam 1978 states "The choice of method (of faradism) appears haphazard and subjective as no data exist indicating success rates". A major problem with faradism is the difficulty of applying an effective muscle stimulating low frequency current without causing pain due to the resistance of the skin and superficial tissue (McGuire 1975)

Interferential Therapy

Interferential therapy is a method of producing a low frequency stimulating current within the body without the problem of overcoming the barrier of skin resistance (Willie 1969). Two different medium frequency currents of around 4,000 c/s are used (thus eliminating skin resistance) and these are applied to the body simultaneously and from different directions. The intensity of the combined current will increase and decrease rhythmically and the frequency of this effect known as the interference effect, is the difference between the two original frequencies. This is called the beat frequency and if kept within the limit of 0-100 c/s then a muscle stimulating current is produced in the area where the 2 medium frequencies mix (Willie 1969) (Figure 1 L). Using this method McGuire (1975) observed that 16 of 24 patients with symptoms of stress incontinence were much improved after 4 weeks of treatment. However, like the previous studies, the evaluation was purely subjective.

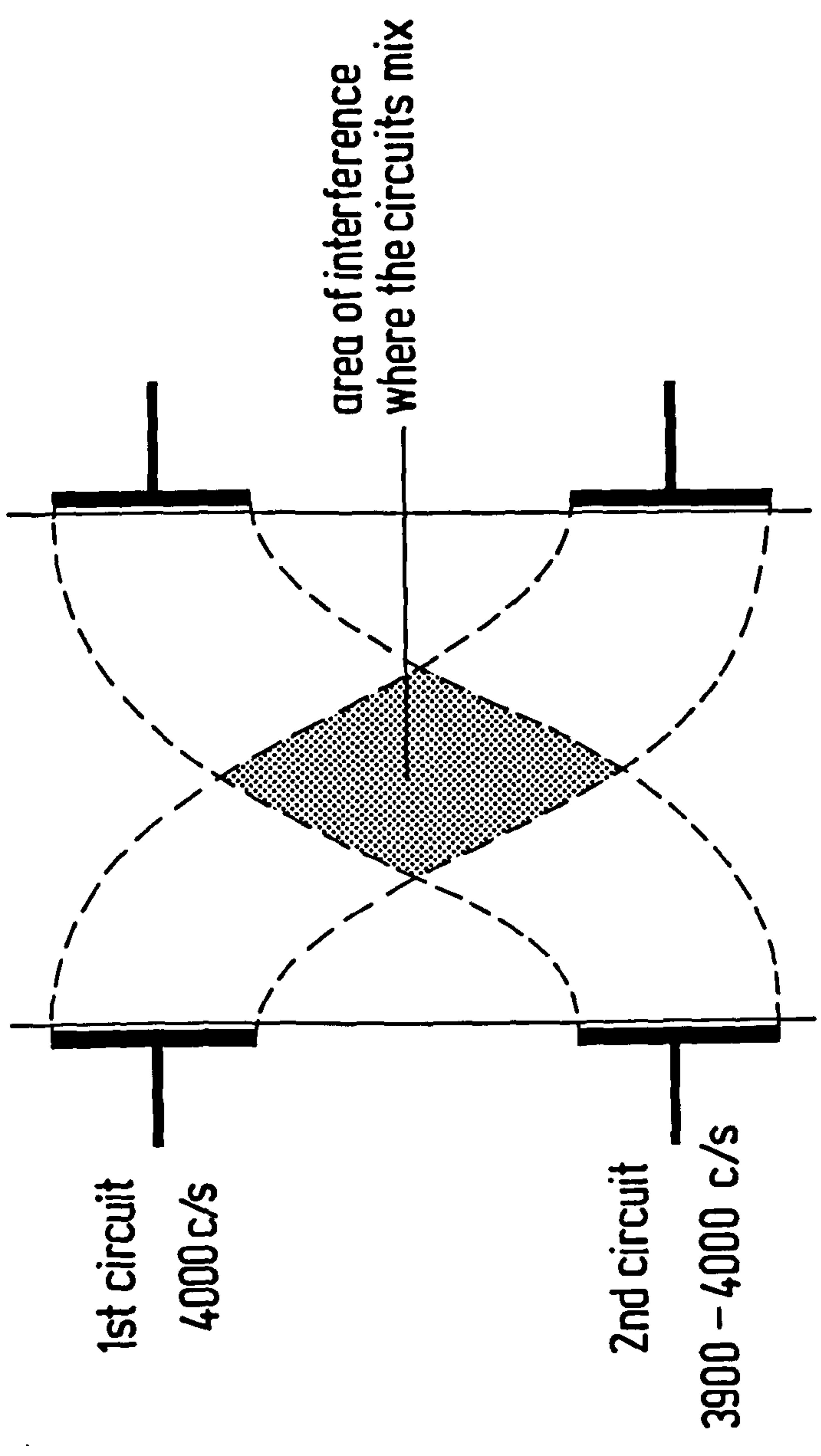


FIGURE 1L - Schematic representation of "Interferential" current,
(The area of low frequency stimulation where the two
medium frequency currents cross).

The excellent subjective results of Kegel (1951) and Jones (1963) with physiotherapy have not been reproduced and most commonly gynaecologists prefer to treat incontinence primarily by surgery. There has been no objective assessment of the use of physiotherapy in genuine stress incontinence, nor a comparison of different methods of muscle stimulation described above.

A prospective study was carried out to assess objectively the value of physiotherapy in genuine stress incontinence (Chapter 6).

1.5 THE ROLE OF OESTROGENS IN GENUINE STRESS INCONTINENCE

The role of oestrogens in genuine stress incontinence is controversial. In this section the evidence relating to sensitivity of the urethra to oestrogens is presented and steroid receptors in the urethra and the lower urinary tract are discussed. The urethral changes that occur after the menopause are outlined along with the effect of the menopause on incontinence. Finally, previous studies of oestrogens in the treatment of genuine stress incontinence are reviewed and assessed.

1.5.1 Sensitivity of the Urethra to Oestrogens

Embryological Association

The lower urinary and genital tract have similar embryological origins. The primitive urogenital sinus gives rise to the vesico-urethral canal and the definitive urogenital sinus. The mucosa of the bladder rises from the endodermal lining of the vesico-urethral canal and the detrusor is derived from its splanchnopleuric mesoderm, (Hamilton and Mossman 1972). The primitive urethra develops also from the vesico-urethral canal and in later development this forms most of the definitive urethra (Craigmyle and Presley 1975). The definitive urogenital sinus gives rise to the whole length of the vagina (Langman 1975) and it may contribute to the distal portion of the definitive urethra (Hamilton and Mossman 1972).

The developmental differences of the distal and proximal urethra are thought to be reflected in the anatomy of the mature urethra (Smith 1979); the proximal urethra is composed of muscle and glandular tissue and is covered by a transitional epithelium continuous with that of the bladder while the distal urethra is a much simpler structure covered by stratified squamous epithelium similar to that covering the vagina (1.1.1).

The trigone is formed by the absorption of the mesonephric ducts into the wall of the bladder and therefore is mesodermal in origin (Langman 1975). However, there is a possibility that with time, this mesodermal lining of the trigone is replaced by endodermal epithelium of urogenital

sinus origin, (Gyllenstein 1949).

Animal Experiments

Zuckerman (1940) showed that some of the tissues derived from the Mullerian and Wolffian systems, the urogenital sinus and the cloacal membrane are sensitive to oestrogen. Under experimental conditions, oestrogens produced a "squamous response" with proliferation, cornification and desquamation of the urethral epithelium of several species. This has also been noted previously by Burns (1939) when oestrogens produced extreme cornification of the opossum urethra resulting in complete urinary obstruction and by Hundley et al (1935) who found that the dog urethral epithelium changed from transitional to squamous after the administration of oestrogens.

Cytohormonal Studies

In the human, the urethra has also been shown to be sensitive to oestrogen by cytohormonal studies. Cytohormonal analysis, a branch of cytology, is based on the maturation effect of oestrogen on the vaginal or urethral squamous epithelium and was first described in the vagina (Papanicolou 1933). This epithelium has three distinct cell layers arising from a basal germinal layer, namely the parabasal, intermediate and superficial layers, and the cellular pattern of a smear taken from the vaginal epithelium reveals the degree of oestrogen activity at that particular time.

Smith (1972) carried out a cytohormonal study of distal urethral smears based on the method of Papanicolou (1933), in 402 females in all 3 stages of sexual life - prepuberty, reproductive and post menopausal. The smears were taken by inserting a small sterilised orange stick into the distal urethra and gently rotating it and spreading the smear cells on to one half of a glass slide. They were also compared with vaginal smears on the other half of the slide. His results showed that the cytology of the urethral squamous epithelium changed with the physiological variations (even those within the menstrual cycle) in oestrogen activity, that occurred in the three stages of sexual life examined. The urethral cytological changes were paralleled by similar changes in the vagina.

Previous cytohormonal studies have been carried out on urinary sediment, the majority of cells of which are derived from the distal urethra (Del Castillo et al, 1949). McCallin, et al (1950) described variations throughout the menstrual cycle and pregnancy, changes in post-menopausal women before and after oestrogen therapy were described by Solomon et al (1958), while a statistical correlation between urinary and vaginal smears was demonstrated by Lencioni (1953).

The Influence of Endogenous oestrogens on the Urethral Pressure Profile

The effect of the menstrual cycle on the urethral pressure profile has been studied in 5 continent females

(Schrieter et al 1976). They found in all cases the pressure profiles increased in mid cycle and decreased pre-menstrually. They attributed this change to varying oestrogen levels though no statistical analysis was performed. In a larger study of 27 healthy nulliparous women, van Geelen (1980) did not find any change in the urethral pressure throughout the menstrual cycle and the pressures were unrelated to serum levels of oestradiol or progesterone. However, he did find a significant correlation between anatomical and functional urethral length and serum oestradiol levels, thus confirming some urethral response.

1.5.2 Steroid Hormone Receptors in the Female Lower Urinary Tract

On the basis of the embryological, animal and cyto hormonal evidence outlined above, the urethra would appear to be sensitive to oestrogens. As mentioned earlier, urethral function may also be influenced by progesterone (1.2.2).

The trigone is also thought to be sensitive to oestrogens. Tyler (1962) found that stratified squamous epithelium was commonly found in the trigone of adult women and that it atrophied with age and underwent cyclical changes during the menstrual cycle similar to the vaginal epithelium. This stratified squamous epithelium of the trigone ("pseudomembraneous trigonitis" or squamous mataplasia) has been postulated as representing a response of the trigonal epithelium to oestrogens (Henry and Fox, 1971, Packham 1971), since it is a rare finding in children and oestrogen administration has caused it to increase in size (Ney and Ehrlich 1955).

Studies of the mechanism of action of steroid hormones in various cells systems have led to the discovery of steroid hormone receptors* (Jensen et al 1967). These are highly specific protein molecules which bind the appropriate

*Footnote: The experimental demonstration of specific cytoplasmic steroid binding proteins has given rise to the use of "receptor" as a convenient short term. Use of the term in this study is not meant to imply the definition of "receptor" as currently used in pharmacology.

hormone with a high affinity and the sensitivity of any tissue for steroid hormones seems to be directly related to the receptor content in the "target" cells.

In the human, specific oestrogen and progesterone receptors have been found in the endometrium and myometrium (Gabb and Stone 1974, Philibert & Raynaud 1974) and oestrogen receptors also have been demonstrated in the fallopian tube (Robertson et al 1975), cervix uteri (Sandborn et al 1975 and 1976), breast (Singh et al 1978) and vagina (Wiegerinck et al 1980). Lindskog et al (1980) have identified oestrogen receptors in the rat urethra (none present in the bladder) with a similar binding capacity to those in the vagina which was about one third of those of the uterus. However, there are no published reports of the presence of steroid hormone receptors in the human female lower urinary tract. In relation to this, a study was carried out to estimate the level of cytosol, oestrogen and progesterone receptors in this site (Chapter 7).

1.5.3 Post Menopausal Changes in the Urethra

Morphology of the Female Urethra in relation to Age

Huisman and Salome (1975) and Huisman (1979) described the morphology of the female urethra in relation to age. 17 preparations from patients aged 0 to 78 years were studied and divided into three age groups corresponding to the neo-natal, fertile and post-menopausal periods. The most significant age changes were related to the submucosal venous plexuses and rich system of arterio-venous anastomoses which were most fully developed in the fertile period but which declined post-menopausally. In the rabbit, these submucosal vessels have been shown to be sensitive to oestrogen as the cross-section of their lumen increased several times under the effect of oestrogen, (Molnar and Nagy 1965). The age change described by Huisman may be related to falling oestrogen levels after the menopause though other factors in the ageing process may also be involved.

The other changes Huisman described with increasing age were an increase in elastic tissue, increase in circular smooth muscle and a decrease in the density and greater diameter variation of the striated muscle fibres.

Smith in his cytohormonal study of age changes in the female urethra in 1972, showed that the distribution of smears in 123 post-menopausal women studied indicated varying levels of oestrogen activity. In 85 the smears had a "crowded menopausal" appearance with intermediate

and para-basal cells indicating a decline in oestrogen activity. 15 had smears showing normal cycle activity indicating full oestrogen activity. In only 23 were there true atrophic smears consisting of parabasal cells indicating the absence of oestrogen activity. There was however, a progressive decline in oestrogen activity with advancing age.

In some post-menopausal women, the oestrogen deficiency may be such as to result in atrophic distal urethritis and stenosis (Smith 1976), and give rise to the "Urethral syndrome" of frequency, urgency and dysuria. This has been successfully treated by systemic oestrogen therapy, with maturation of the atrophic urethral smears (Smith, 1976).

Urethral Pressure Profile and Age

The amplitude of the urethral pressure profile decreases with age (Edwards and Malvern, 1974, Plante and Susset, 1980). Edwards and Malvern estimated the mean maximum urethral pressure to be 83 cm of water in normal patients aged 21 to 30 years and this fell to 42 cm of water in the age group 60 to 70 years. Plante and Susset, (1980), attributed this decrease to a loss of urethral elasticity while Osborne (1976) stated that it was due at least in part to the decreasing vascularity of the peri-urethral tissues associated with falling oestrogen levels. However, no evidence was presented for either of these statements.

1.5.4 Effect of the Menopause and Oestrogen Deficiency On Incontinence

Oestrogen deficiency following the menopause is thought to be a contributory factor in genuine stress incontinence, (Hald, 1975; Stanton 1977). Hald (1975) postulated that oestrogen deficiency may cause atrophic changes in the urethral mucosa, vasculature, supporting ligaments and pelvic floor and hence cause incontinence, though no evidence was presented for this.

Osborne, (1976) studied by questionnaire 600 women aged between 35 and 60 years working for a chain store in the United Kingdom. He found an incidence of stress incontinence of 26% and this did not change significantly with either age or the menopause. Brocklehurst et al (1972) also found a lower incidence of stress incontinence (23%) in patients in a general practice aged over 65 years in comparison to patients aged 45 to 64 years (57%). Thomas et al (1980) in their general practice postal survey found there was no change in the overall prevalence of regular incontinence in women aged between 35 and 64 years.

Although many factors in ageing can influence incontinence the above studies indicate no significant effect of the menopause on incontinence. While oestrogen deficiency can cause urethral changes (1.5.1, 1.5.3) its relationship to incontinence is still not clear.

1.5.5 The Treatment of Genuine Stress Incontinence with Oestrogens

There have been many published reports of the treatment of genuine stress incontinence with oestrogens and these are reviewed below. They have been divided for clarity into controlled and non-controlled studies and further sub-divided on whether a subjective or objective assessment of the results was made.

Non-Controlled Subjective Studies

The most salient of these have been summarised:

1. Salmon et al (1941) treated 16 post-menopausal patients complaining of either incontinence (10) or the urethral syndrome (6) with systemic oestrogen therapy (estradiol benzoate or dipropionate). After 4 weeks of treatment 13 out of the 16 were asymptomatic.
2. Eckerling and Goldman (1972) carried out a long term assessment (up to 10 years) of the results of local and systemic oestrogen therapy given to 195 post-menopausal women with the complaints of utero-vaginal prolapse and stress incontinence. 63% of the patients were much improved, 27% improved and 10% no better after treatment and in 83% of cases, oestrogens alone were felt to be sufficient treatment.

3. Musiani (1972) reviewed several previous studies of quinestradiol (3-cyclopentyl ether of oestriol) in the treatment of female incontinence. Along with 34 of his own patients, 110 women had received quinestradiol therapy and 36 were reported cured and 43 improved.

All these reports suffered from the limitations of non-controlled studies coupled with lack of objective assessment.

Non-Controlled Objective Studies

Caine and Raz (1973) studied the affects of oestrogens and progesterones in 50 post-menopausal women with stress incontinence. 40 patients received premarin (conjugated equine oestrogens) and 10 medroxyprogesterone acetate. After treatment a subjective assessment was made and urethral pressure profiles (Brown and Wickham 1969) and urethral vascular pulsations (Enhorning 1961) were recorded. Incontinence ceased or improved in 26 out of the 40 oestrogen treated patients and this was related to increased urethral pressure profiles and vascular pulsation. In comparison, 6 out of the 10 progesterone treated patients deteriorated and there was an associated reduction in the urethral pressure profile. The beneficial effect of oestrogens was speculated to be achieved by improving the hermetic closure of the urethral mucosal lining, by affecting the adrenergic response of the urethral smooth muscle and by altering the submucosal vascular component of urethral closure.

Schreiter et al (1976) assessed the sensitivity of alpha receptors in the urethral musculature by studying the urethral pressure profile in 5 continent and 3 stress incontinent females. In both groups of patients there was a rise in the urethral pressure profile after administration of the alpha stimulator phenylephrine and after 10 days of treatment with 2 mgs oestriol t.d.s. there was a further increase in the profile. This was interpreted as increased sensitivity of the alpha receptors by oestrogen as postulated by Caine and Raz (1973).

Harrison (1976) also studied the effect of systemic oestrogens on the urethral pressure profile in 10 patients attending the Menopause Clinic at Chelsea Hospital for Women. 4 patients showed a significant difference after therapy, however in only one case was there an increase in the mean pressure, in the other three there was a significant fall in pressure - a finding which is difficult to explain.

Controlled Subjective Studies

Judge (1969) treated 20 geriatric incontinent patients (no assessment of type of incontinence was made) with quinestradiol or placebo in a double blind cross over trial. By the 5th week of treatment with quinestradiol there was a significant reduction in the frequency of incontinence (number of times incontinent/week) in comparison to the placebo period though no patient became completely continent.

Controlled Objective Studies

13 postmenopausal women with a urodynamic diagnosis of genuine stress incontinence were treated with oestradiol valerate for one month and thereafter with oestradiol in combination with norephedrine and placebo according to a double-blind cross over regime (Ek et al 1977).

Oestradiol had no affect on the symptom of stress incontinence or urethral closure pressures. Norephedrine in combination with oestradiol had a significant therapeutic effect on the symptom of stress incontinence which correlated to a significant increase in urethral closure pressures. However norephedrine in combination with oestradiol did not increase the urethral pressure profile more than norephedrine alone.

Walter et al (1976) studied 29 females with genuine stress incontinence in a double blind trial. 15 patients received oestrogens (oestradiol 2 mg + estriol 1 mg daily) and 14 received placebo for 4 months. The patients were assessed subjectively and objectively with urethral pressure profiles, cyto hormonal analyses of urethral and vaginal smears and by trigone biopsies. In the oestrogen treated group there was a significant reduction in the symptoms of frequency and urgency, however, there was no significant change in either the symptom of stress incontinence nor in the urethral closure pressure. The influence of oestrogens on the mucosa of the urethra, vagina and trigone was also demonstrated.

In summary, in the treatment of genuine stress incontinence, the evidence is conflicting that oestrogens are effective. To ascertain further the role of oestrogens in this condition, a prospective double blind trial was conducted to evaluate the effect of piperazine oestrone sulphate (Harmogen) on post-menopausal women presenting with genuine stress incontinence (Chapter 8).

CHAPTER 2

THE ROLE OF THE POSTERIOR

PUBO-URETHRAL LIGAMENTS IN THE

AETIOLOGY OF GENUINE STRESS INCONTINENCE

CHAPTER 2

2.1 INTRODUCTION

The posterior pubo-urethral ligaments are considered to contribute to urethral support and it has been suggested that defects of these structures may predispose to genuine stress incontinence (1.2.5). Studies of the gross and histological structures of these ligaments have been performed (Krantz, 1951, Zacharin, 1963, Milley and Nichols, 1971, Albers, 1973), but electron microscopy and neurohistochemistry have not as yet been applied to examine their micro-structure and possible innervation. In view of their possible functional and clinical significance these newer techniques have been used to compare the morphology in specimens obtained from continent and genuine stress incontinent females. The aim was to determine if altered morphology in these ligaments was related to genuine stress incontinence.

2.2 MATERIALS AND METHODS

2.2.1 Specimens

Biopsy samples of the posterior pubo-urethral ligaments were taken from 9 genuine stress incontinent patients at the time of the colposuspension procedure (Burch, 1968). The diagnosis of genuine stress incontinence had been made previously by synchronous video pressure flow cystourethrography (3.2.).

Biopsy samples of the ligaments were also obtained at post mortem from 7 females aged 19 - 84 years with no history of incontinence. In one patient the bladder, proximal and mid-portion of the urethra with attached pubo-urethral ligaments were dissected and removed intact. Serial transverse sections were cut to gain further information on the insertion of the ligaments. In addition, 3 specimens of the ligaments were taken from continent patients having surgery for other gynaecological indications.

All samples were processed for light and electron microscopy. The morphology, histochemistry and fine structure of the specimens from the 9 incontinent patients were compared with the ten "control" samples from the continent females.

2.2.2 Light Microscopy

Each sample was aligned on a cryostat tissue holder and rapidly frozen in 2-methylbutane cooled in liquid nitrogen. Serial sections 10 - 20 μ m thick, were cut in a cryostat maintained at -25°C internal temperature and processed either for routine histology using Masson's trichome technique, for tissue cholinesterases (Gomori, 1952), or catecholamines (Spriggs et al 1966) as outlined below.

2.2.3 Tissue Cholinesterases

Gomori's (1952) method was employed for the demonstration of tissue cholinesterases. Some sections were pre-incubated at 20°C for $\frac{1}{4}$ hour at pH 7.4 in either 10^{-5}M TIPA (tetraisopropylyphosphoramidate) or BW 62C47. All sections were placed in stock solution at pH 6.0 containing either acetyl thiocholine iodide or butyryl thiocholine iodide as substrate together with the appropriate inhibitor in a concentration of 10^{-5}M . Following incubation at 37°C for 3 to 24 hours, sections were washed in distilled water, counterstained with haematoxylin, dehydrated, cleared and mounted in Depex.

2.2.4 Tissue Catecholamines

The method employed was similar to that described for cryostat sections by Spriggs et al (1966). Appropriate sections, adjacent to those processed for the demonstration of tissue cholinesterases, were placed on

glass coverslips, rapidly transferred to desiccators containing phosphorous pentoxide and stored for 1½ to 2 hours. The coverslips were then placed in closed vessels each containing 6 gm of paraformaldehyde previously equilibrated in an atmosphere of 40.5 per cent relative humidity. Sections were then heated at 80°C for 1 to 2 hours, mounted under liquid paraffin and examined in a Vickers photomicroscope using a Wotan HBO 200 W mercury vapour lamp together with excitor filter BG 12/5 mm and barrier filters GG 4/1.5 mm and Wratten 2E.

2.2.5 Electron Microscopy

Small tissue pieces from each biopsy sample were fixed in 2.5 per cent glutaraldehyde on 0.1 M sodium cacodylate buffer at 4°C and pH 7.3 for 2 hours (Sabatini 1963) or 3 per cent potassium permanganate in acetate veronal buffer at 4°C and pH 7.3 for one hour (Richardson 1966). Tissues fixed in glutaraldehyde were subsequently post-fixed in 1 per cent osmium tetroxide in acetate veronal buffer at 4°C and pH 7.3 for 30 minutes (Palade 1952). Following fixation, tissues were dehydrated in ethyl alcohol and embedded in epoxy resin. Thin sections were cut, double stained with alcohol uranyl acetate (Watson 1958) and lead citrate (Reynolds 1963) and examined in a Philips EM 300 electron microscope.

2.3 RESULTS

The biopsy samples obtained from the incontinent patients were identical in the morphology, histochemistry and fine structure to the control specimens. Therefore the following description applies to all specimens.

2.3.1 Macroscopic Appearance

These bilateral ligaments formed white flat pyramidal-shaped structures which had a narrow apical attachment to the pelvic surface of the body of the pubis just lateral to the symphysis approximately at the junction of the lower one-fifth with the upper four fifths of the bone. The ligaments ran backwards and downwards to attach to the urethra at the junction of the proximal and middle thirds; part of the ligament extending to the bladder base. Laterally the ligaments blended with levator ani fascia and medially their margins were almost in opposition. Their length varied from 10 - 15 mm approximately and on average their width was 5 mm (Figure 2A).

2.3.2 Histology

Distributed throughout the thickness of the ligament, smooth muscle bundles were readily identified (Figure 2B). The direction of the majority of these bundles lay parallel to the longitudinal axis of the ligament. Each muscle bundle was surrounded by a matrix of dense connective tissue elements. There was no evidence of any elastic tissue nor striated muscle.

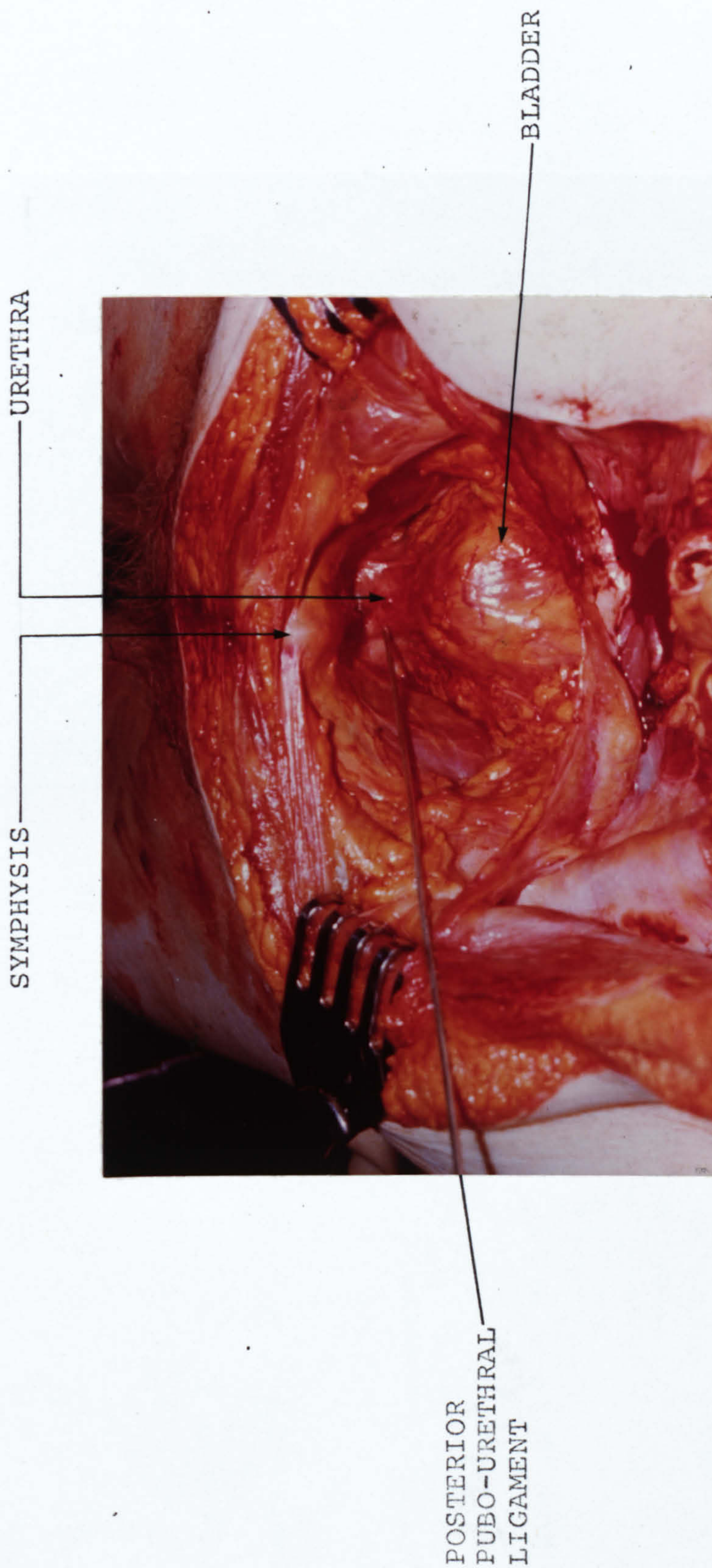


FIGURE 2A - Dissection of the Retropubic Space (of Retzius) at Postmortem with pointer indicating left Posterior Pubo-Urethral Ligament.

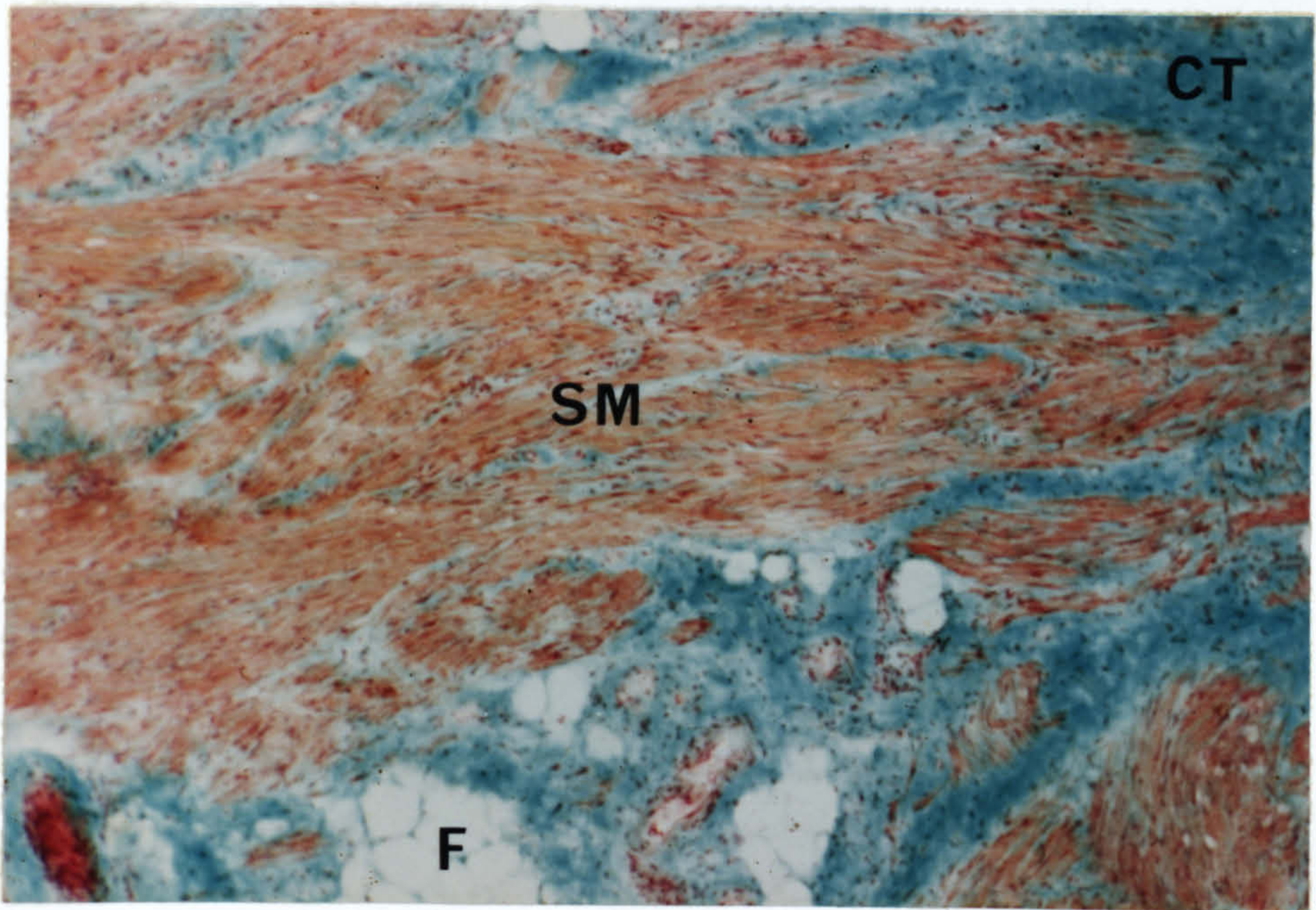


FIGURE 2B - Tissue section processed with Masson's trichrome showing Smooth Muscle bundles (SM), Connective Tissue (CT) and fat (F).

Examination of the serial transverse sections of the bladder neck and urethra showed that the ligament had its maximum insertion into the proximal third of the urethra with extensions to the middle of the urethra and bladder base (Figure 2C).

2.3.3 Tissue Cholinesterases

The constituent cells of each muscle bundle within the ligaments were devoid of both acetyl and pseudo-cholinesterase. However, numerous acetyl-cholinesterase positive (presumptive cholinergic) nerve fibres were observed forming a uniformly rich plexus within each of the muscle bundles (Figure 2D). Similar nerves were also observed forming perivascular plexuses around large blood vessels.

2.3.4 Tissue Catecholamines

Other than for perivascular nerves, the technique for tissue catecholamines failed to demonstrate any noradrenaline-containing nerve fibres within the smooth muscle bundles of these ligaments (Figure 2E).

2.3.5 Electron Microscopy

The fine structural features of the muscle cells within the pubo-urethral ligaments was similar to those of smooth muscle in other regions of the lower urinary tract (Gosling and Dixon 1975). Each cell contained a centrally placed ovoid nucleus surrounded by numerous longitudinally

orientated myofilaments interspersed by occasional mitochondria and dense bodies (Figure 2F). Rows of caviolae occurred at the surface of each cell, and peg and socket junctions were frequently seen between adjacent cells.

It is now generally accepted that two types of autonomic nerves can be recognised electron microscopically. This distinction is based upon the fine structure of the axonal vesicles contained within the nerve terminal. Noradrenergic axons contain numerous small (40 - 60 nm diameter) vesicles which possess a central electron dense core while presumptive cholinergic axons possess vesicles of a similar size but which are invariably agranular (Gosling and Dixon, 1975). In all the specimens presumptive cholinergic terminals were frequently encountered between individual smooth muscle cells (Figure 2G). Axons containing small dense vesicles characteristic of noradrenergic nerves were not observed in the smooth muscle bundles.

POSTERIOR PUBO-URETHRAL LIGAMENT

URETHRAL STRIATED MUSCLE

URETHRAL SMOOTH MUSCLE

URETHRAL LUMEN

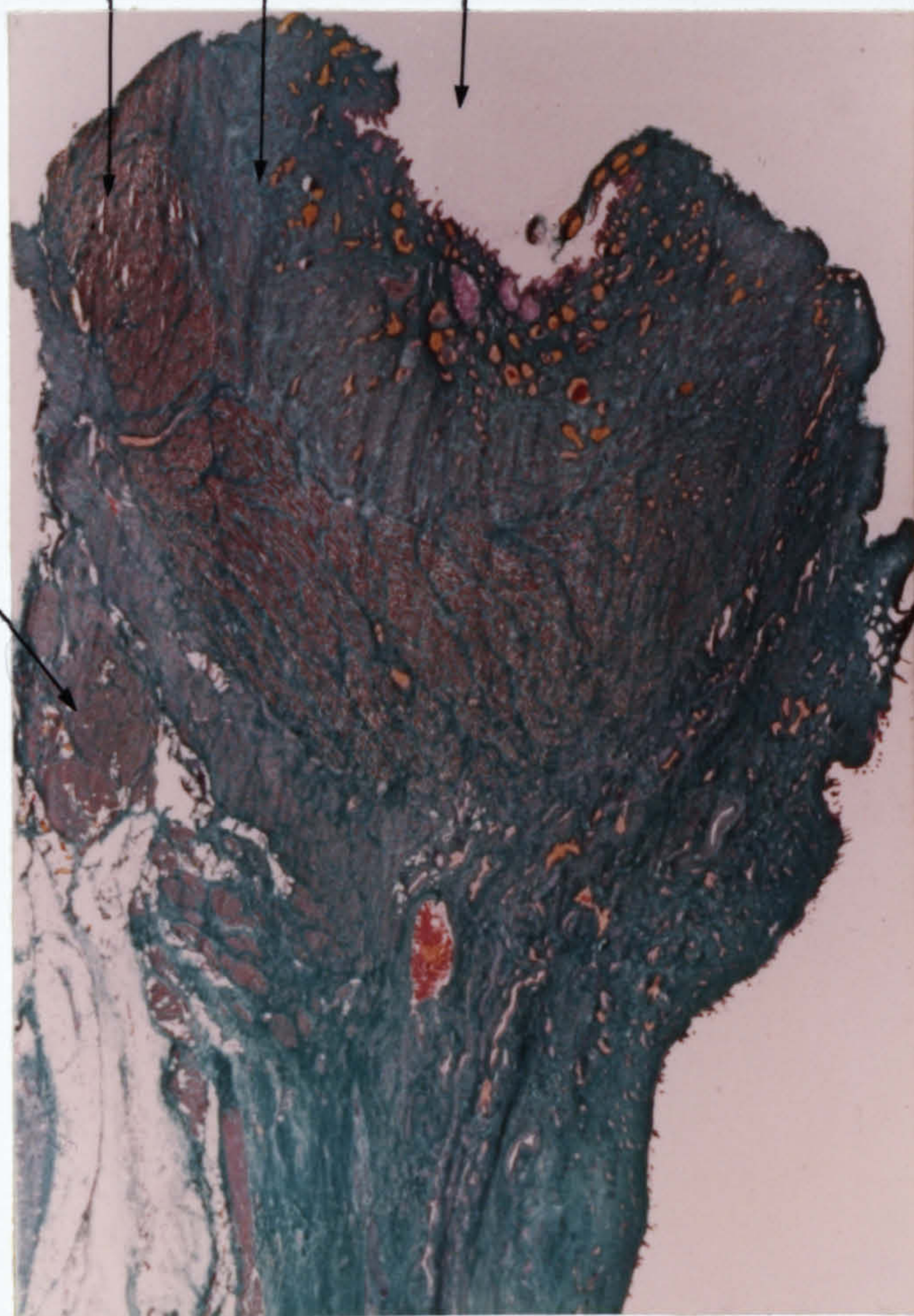


FIGURE 2C - Transverse Section of the Urethra at the junction of the Proximal and Middle third showing the Posterior Pubo-Urethral Ligament immediately distal to its maximum insertion into the Proximal Urethra (Masson's Trichrome Stain).

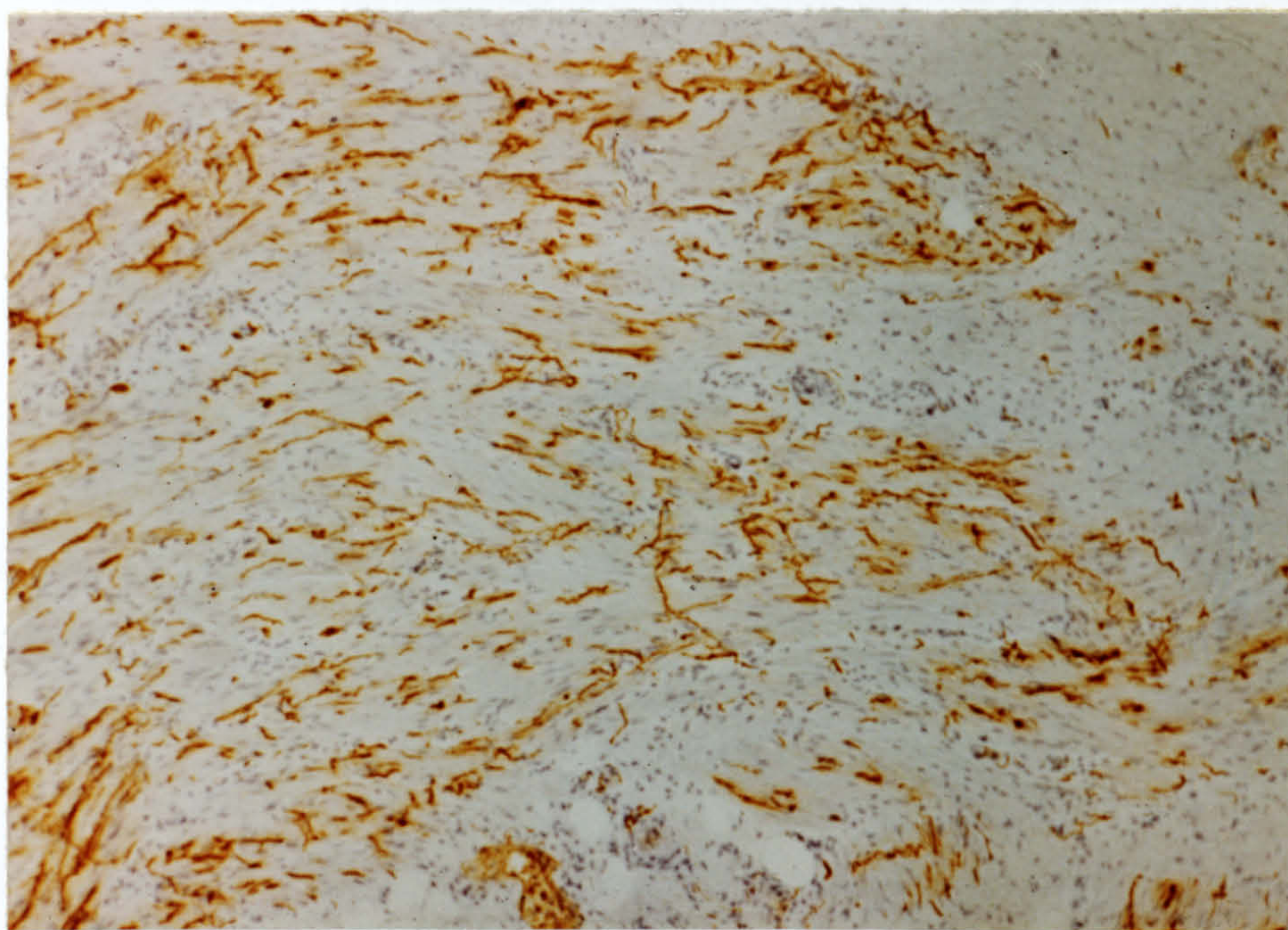


FIGURE 2D - Adjacent Tissue section (to Figure 2B), inhibited to show Acetyl-Cholinesterase, illustrating numerous Acetyl-Cholinesterase positive (presumptive cholinergic) nerves within the Smooth Muscle bundles of the ligament.

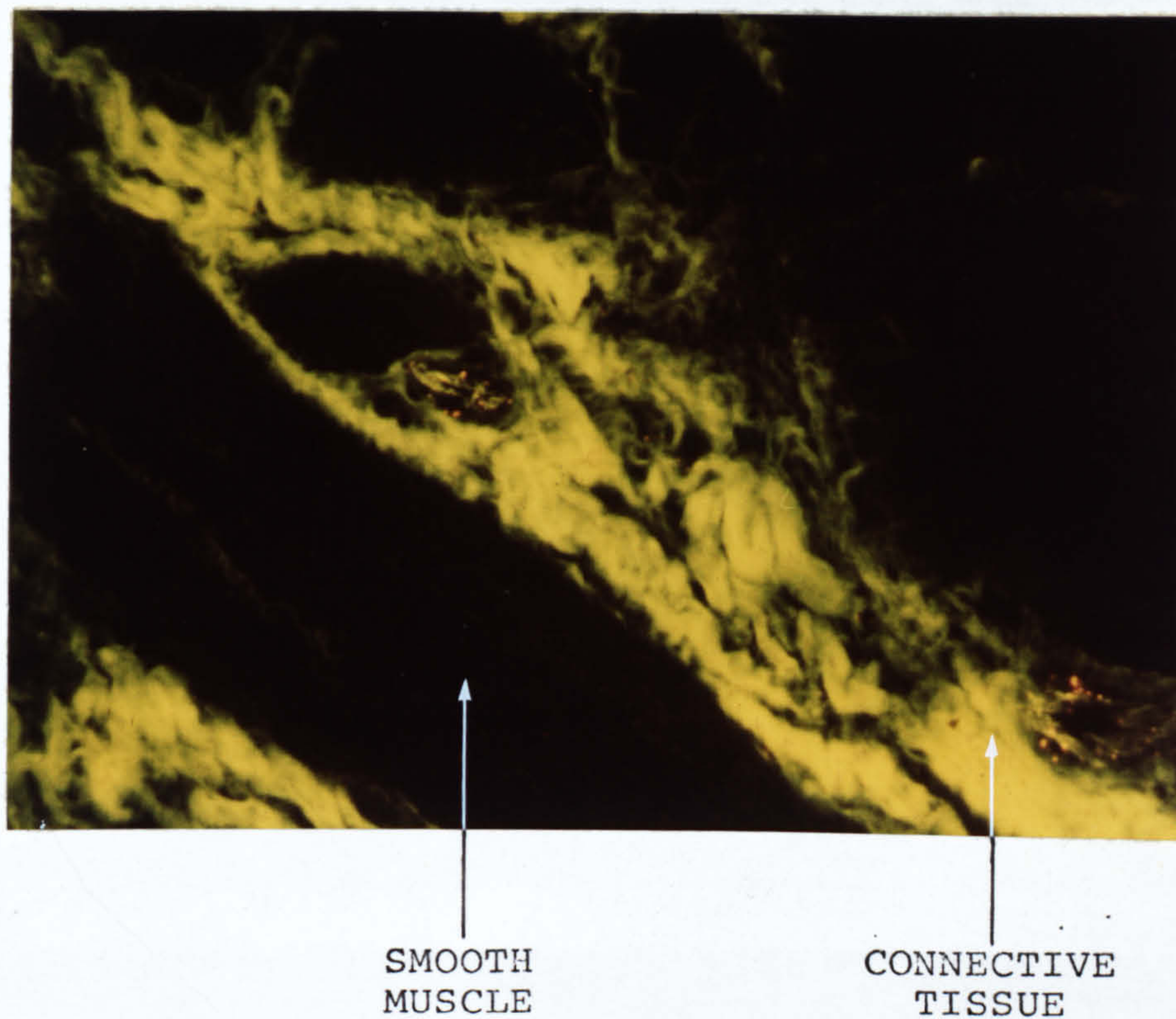


FIGURE 2E - Fluorescent preparation for the demonstration of Noradrenergic nerves. No fluorescent (noradrenergic) nerves are seen within the Smooth Muscle bundles of the ligament.

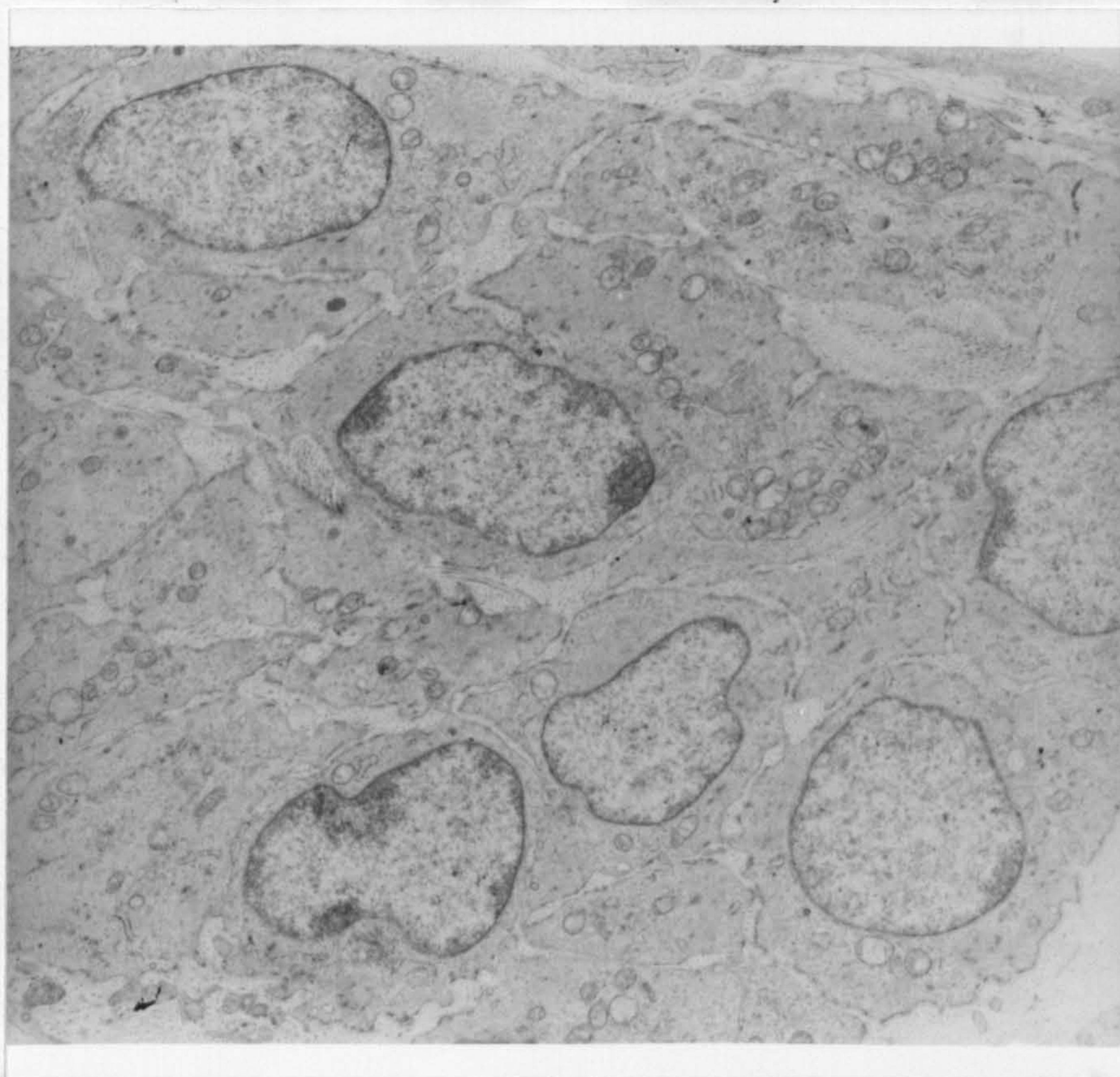


FIGURE 2F - Electron Micrograph showing the fine structure of the Smooth Muscle Cells in the ligament (X5,500).

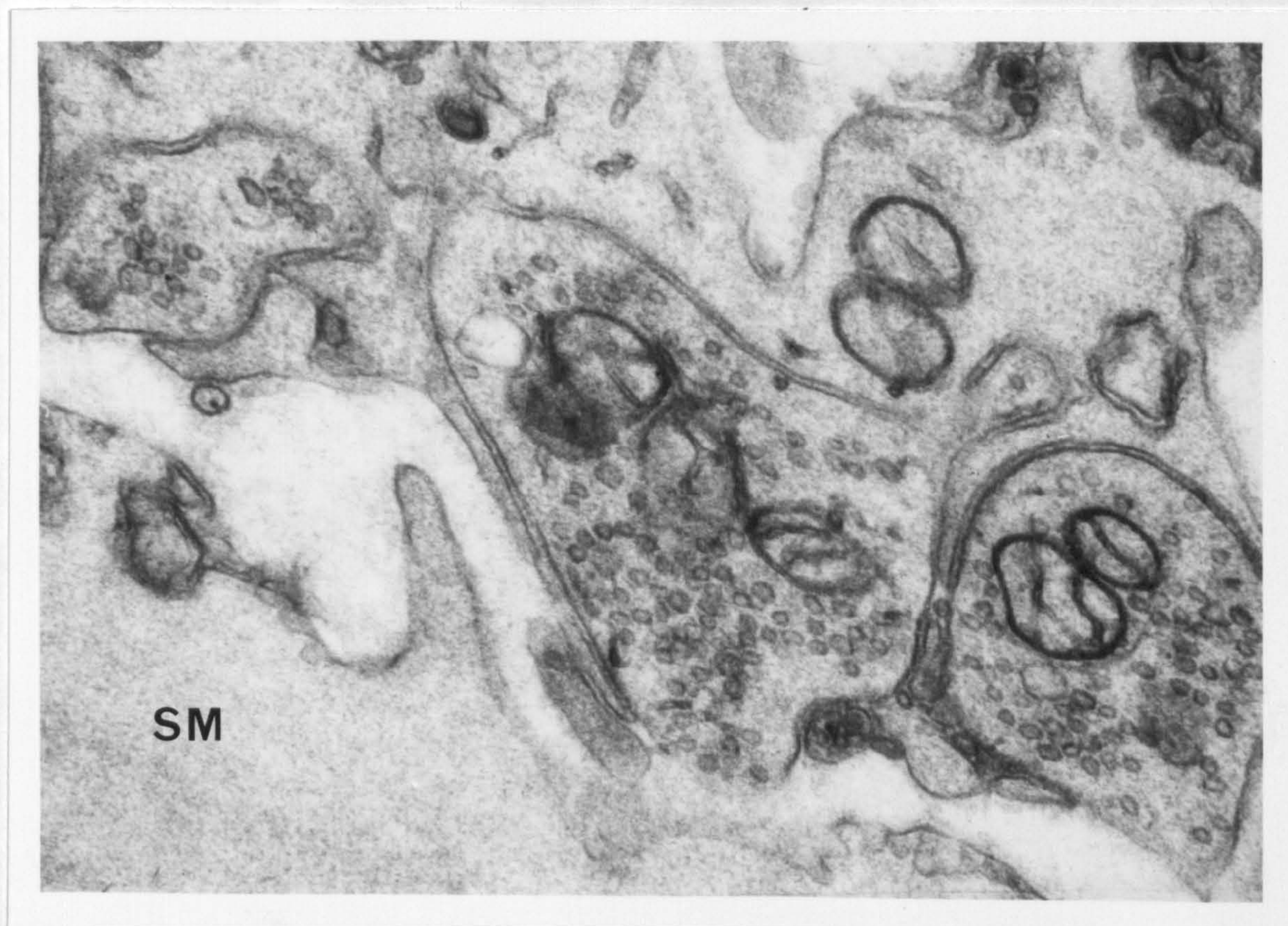


FIGURE 2G - Electron Micrograph showing several cholinergic nerve terminal regions, packed with small agranular vesicles (X28,500) adjacent to Smooth Muscle Cell (SM) of the ligament

2.4 DISCUSSION

The similarity in the morphology and autonomic innervation of the specimens of the posterior pubo-urethral ligaments from the control and incontinent patients indicates that it is unlikely that altered morphology of these ligaments is an aetiological factor in genuine stress incontinence. The possibility of a functional disturbance of the ligaments contributing to genuine stress incontinence has not, of course, been excluded, but the results of this study have not substantiated the theory that defects of these structures predispose to genuine stress incontinence (Krantz 1951, Zacharin 1963).

The present study has shown that in addition to collagen, the ligaments contain a marked smooth muscle component which is associated with nerves, the enzyme content and fine structures of which are similar to those believed to represent cholinergic autonomic nerves. Consequently, the term "ligament" may be a misnomer as these structures contain contractile elements under neural control. Their rich presumptive cholinergic innervation is very similar to that of the detrusor muscle. On the basis of this evidence, it is possible that at the time of detrusor contraction the pubo-urethral ligaments are also subjected to neural stimulation so that they may play an active role in stabilising the proximal urethra or assisting bladder neck opening during voiding. It is interesting to note that Power (1954) using radiographic data suggested that "the pubo-vesical structures (i.e.

these ligaments) have not only a suspensory task but also an important function in the opening of the internal vesical os". Experimentally also the cat proximal urethra opens with para-sympathetic stimulation, (Elliot, 1907, Girado and Campbell, 1959). However McGuire (1979) points out that cholinergic discharge also may result in urethral contraction with urethral shortening resulting in the urethra pulling itself open, or the detrusor itself may contribute to urethral opening by pulling on the urethral musculature by virtue of the arrangement of the detrusor and urethral smooth muscles at the bladder neck. Attractive as the theory is, of the pubo-urethral "ligaments" assisting bladder neck opening during micturition, further work is clearly needed before this hypothesis can be substantiated.

CHAPTER 3

METHODS OF URODYNAMIC INVESTIGATION

3.1 URODYNAMIC CLINIC AND PATIENT FLOW CHART

All the patients in the conservative treatment studies were seen initially at the Urodynamic Clinic, University Hospital of South Manchester (UHSM). This is a multi-disciplinary clinic incorporating the specialties of gynaecology, urology and geriatric medicine. The patients were referred from several sources but principally from local general practitioners, from other specialties in UHSM and also from surrounding Hospitals in the North West of England.

At the initial clinic attendance a full history was taken on a specially designed questionnaire and a general, pelvic and where indicated neurological examination carried out. Every patient completed a bladder chart recording voiding times and pad or pant changes for 24 hours for 7 days before their clinic visit (1.3.2). A mid-stream specimen of urine for culture and sensitivity was taken from every patient and an independent flow rate was carried out in privacy using a DISA flowmeter (1.3.4).

Thereafter the patients were investigated by synchronous video pressure flow cystourethrography and some by the Fluid Bridge Test. Those women who were diagnosed to have genuine stress incontinence with stable detrusor function and with no outlet obstruction were recruited into the conservative treatment studies.

The physiotherapy study initially included all the

consenting genuine stress incontinent patients. However once the oestrogen study for post-menopausal women started, only pre-menopausal women plus those unwilling or those for whom oestrogens were contra-indicated, entered the physiotherapy trial thus introducing a degree of age bias in patient selection towards the end of this study.

In both the conservative treatment studies as well as being assessed subjectively, the patients were also assessed objectively by bladder charts, urethral pressure profiles and the Urilos Nappy Test. This is summarised in the patient flow chart Table 3A and the methods of urodynamic investigation employed are described in the next section.

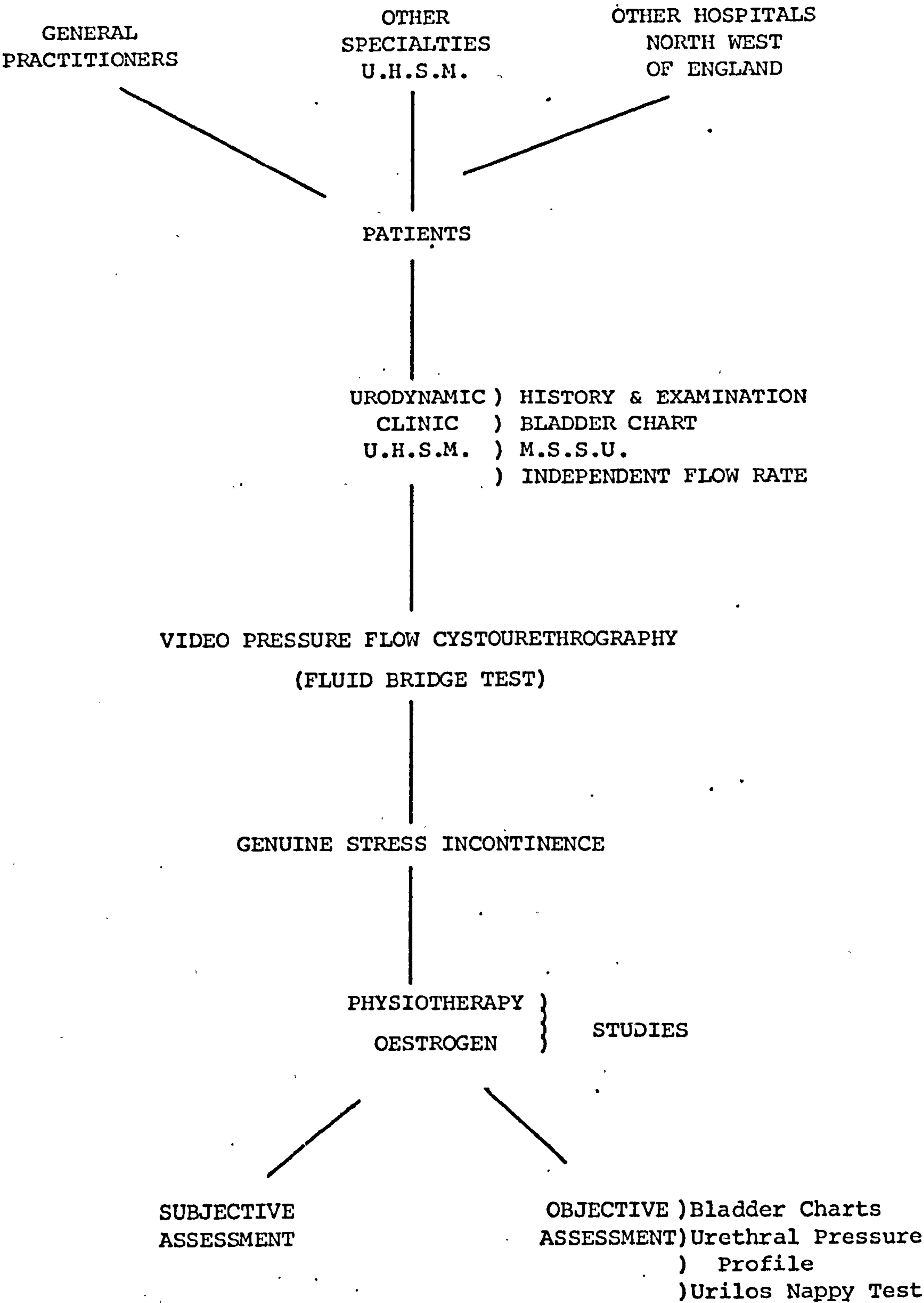


TABLE 3A: PATIENT FLOW CHART

3.2 SYNCHRONOUS VIDEO PRESSURE FLOW CYSTOURETHROGRAPHY

3.2.1 Apparatus

A Hewlett-Packard six channel chart recorder was used and recorded:

1. The intravesical pressure via a 1.65 mm fluid-filled polythene cannula introduced into the bladder via the urethra and connected to a Bell and Howell pressure transducer.
2. The rectal (intra-abdominal) pressure by a similar cannula protected from faecal blockage by a finger stall.
3. The electronic subtraction of the rectal from the intravesical pressure to give the detrusor pressure.
4. The filling volume measured by means of a strain gauge weighing transducer.
5. Volume voided and flow rate via a modification of the Von Garrelts meter (1.3.4).

A television camera situated above the paper trace viewed intravesical pressure, detrusor pressure and flow rate. These were mixed electronically with the radiographic image of the bladder and recorded on another

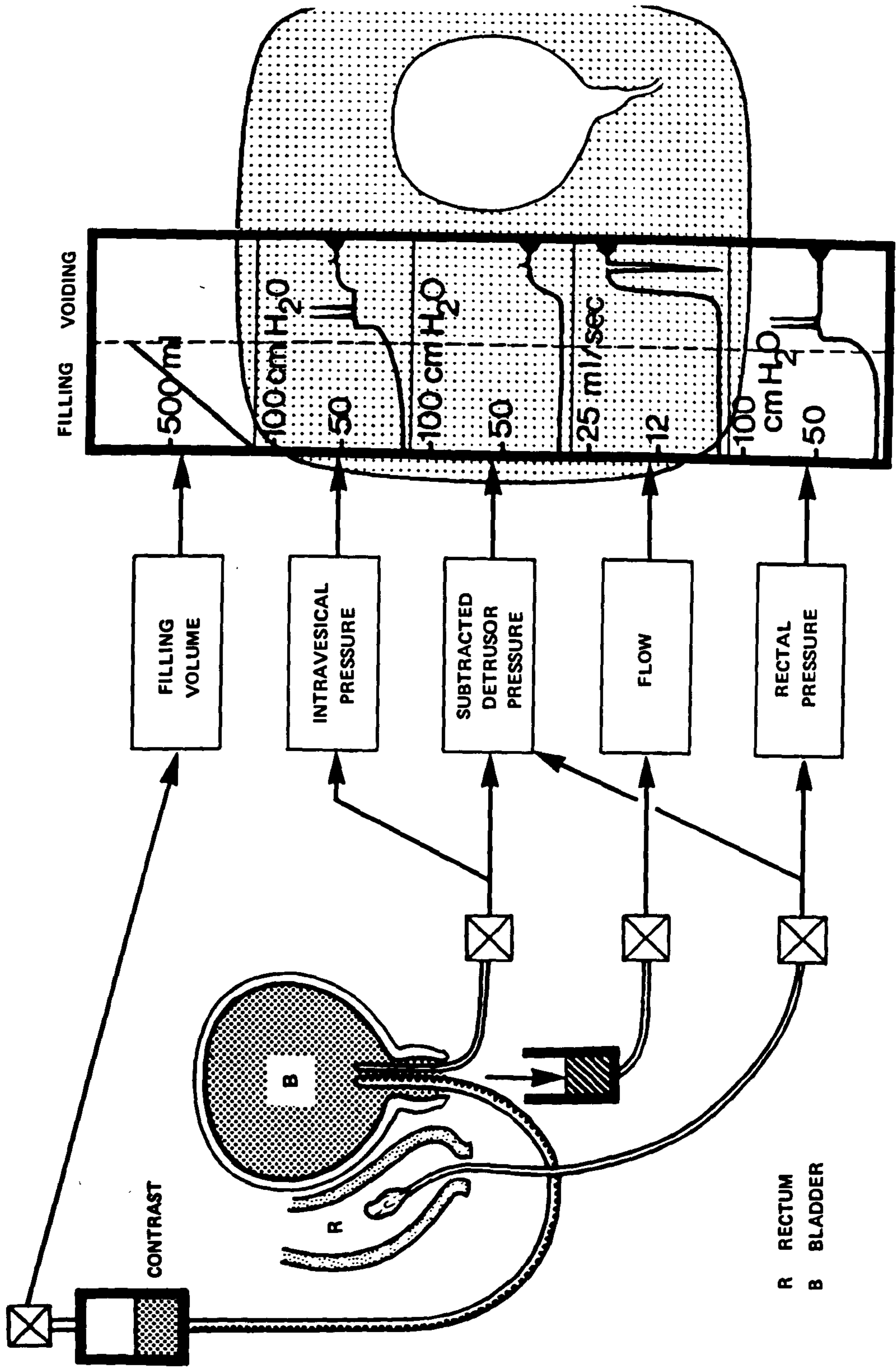


FIGURE 3A - Schematic representation of Synchronous Video Pressure Flow Cystourethrography.

monitor, (Figure 3A). This combined image was recorded on videotape together with a simultaneous sound recording of the instructions given to the patient.

3.2.2 Technique

The patient first voided outside in privacy and then lay on a tilting x-ray table. The external genitalia and urethral meatus were cleansed with 1% savlon. Using a sterile technique, 12 gauge urethral and 1.65 mm external diameter polythene catheters were introduced into the bladder per urethrum^a. Before insertion, the tip of the small catheter was lodged firmly within the distal eye of the urethral catheter and once inside the bladder, the smaller catheter was pulled back until they were felt to disengage. Both catheters were then pushed further into the bladder and any residual urine was measured. A similar polythene cannula protected by a finger stall from faecal blockage was introduced into the rectum. The two narrow catheters were then connected to the Bell and Howell pressure transducers which were flushed through with sterile water to exclude any air from the system. The transducers were fixed in a transducer stand, the height of which was altered to be level with the patients pubic symphysis at all times. The patient was then asked to cough 2 or 3 times firstly to check that there was no air in the system and secondly to check that subtraction was accurate.

The procedure was explained carefully to the patient

and she was instructed not to attempt to void under any circumstances until she was specifically asked to do so. Supine rapid fill cystometry at 100 mls per minute was performed using 25% diodone at room temperature. The patient indicated her first desire to void and again when her bladder was absolutely full. Filling was then stopped and the patient was screened in the supine position and asked to cough several times. Any leakage of urine, opening of the proximal urethra or descent of the bladder base was noted. The screening table was then tilted to the erect position to observe the effect of "passive posture change" on detrusor activity.

The contrast reservoir was then lowered and the patients bladder emptied back into it by gravity. Filling cystometry was then repeated as before but in the erect position. At maximum bladder capacity the filling catheter was removed and the patient screened in the oblique erect position. The effect of coughing was again noted. She was then allowed to void into a hand held funnell connected by tubing to the flow meter and the maximum voiding pressure, peak flow rate and volume voided were recorded (Figure 3B). When voiding was fully established the patient was asked to stop the stream and her ability to milk-back urine from the proximal urethra into the bladder was assessed. She was then allowed to completely empty the bladder and any residual urine volume was noted.

34% of the patients were unable to void in the standing position and these patients were seated on a commode nearby while still connected to the pressure

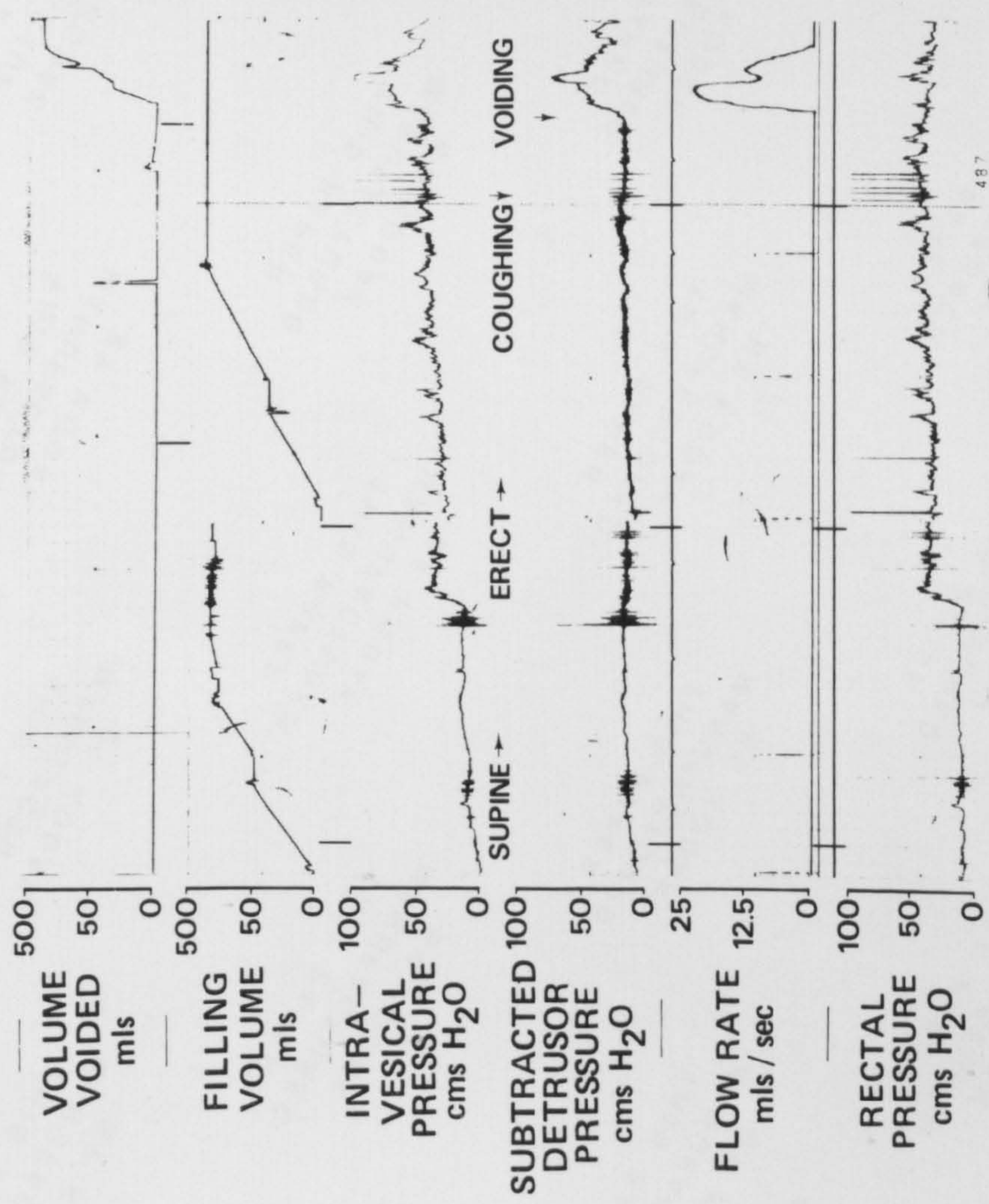


FIGURE 3B - Normal Cystometry and Voiding.

measuring catheters. The flow rate, volume voided and volume pressure were recorded.

In summary, the stability of the detrusor muscle on the patients in the studies was assessed by many "provocative tests", i.e.

- | | |
|--|-------------------|
| 1. Rapid-fill cystometry | } While lying |
| 2. Coughing at maximum capacity | |
| 3. Passive posture change from supine to erect position. | } Supine. |
| 4. Repeat rapid-fill cystometry | } While standing. |
| 5. Coughing at maximum capacity | |
| 6. Filling catheter withdrawal | |

Detrusor instability was diagnosed when there was a rise in detrusor pressure of greater than 15 cm of water (ICS, 1976), (Figures 3C, 3D). A retrospective study (Chapter 4) was carried out to assess the contribution of these tests in provoking detrusor instability and to evaluate postural cystometry and the effect of age.

Genuine stress incontinence was diagnosed by the absence of involuntary detrusor contractions and by the presence of an open proximal urethra either at rest or coughing without leakage of urine (Grade 1) or when leakage was visualised (Grade 2), (Whiteside, 1973), (Figure 3E).

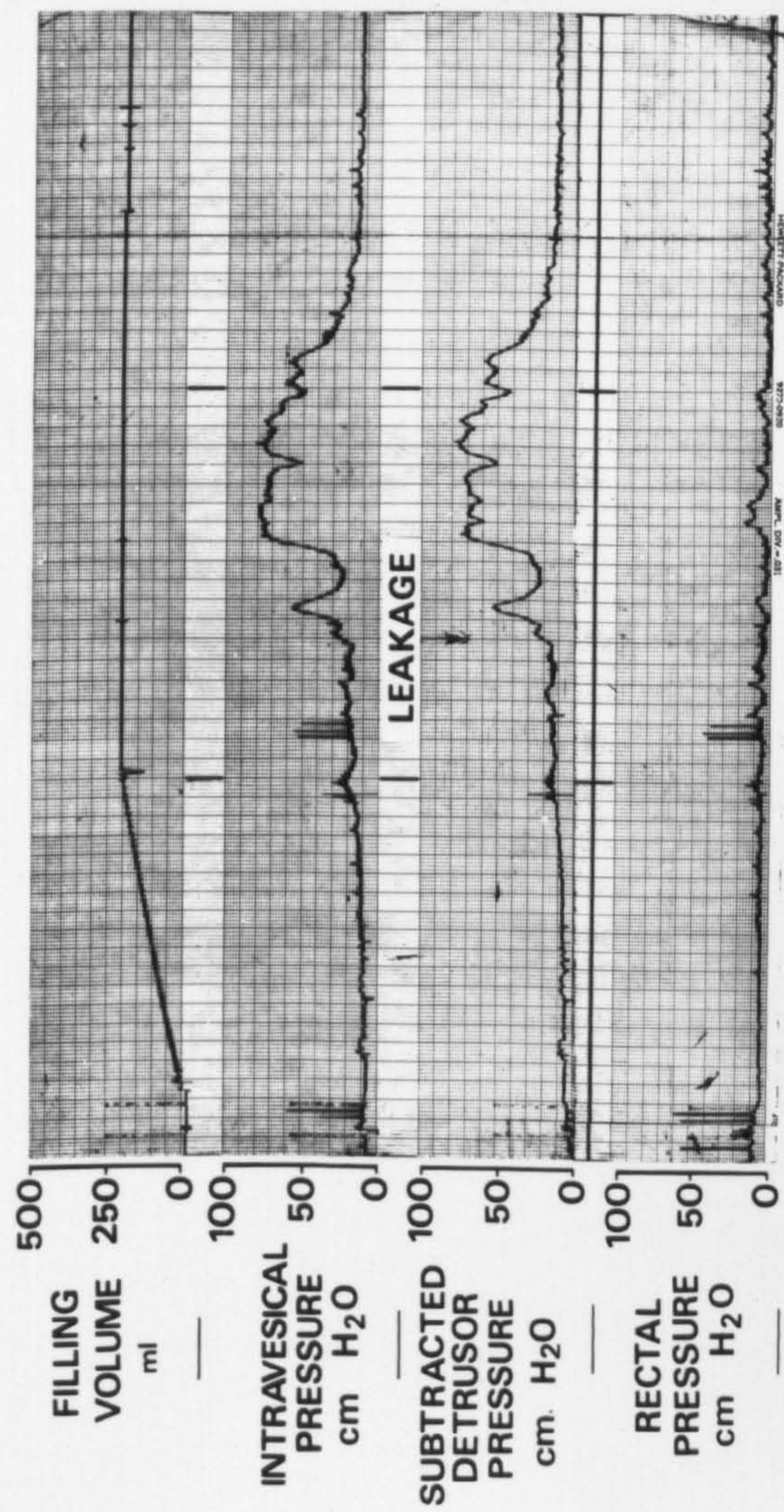


FIGURE 3C - Detrusor Instability : Filling Provoked.

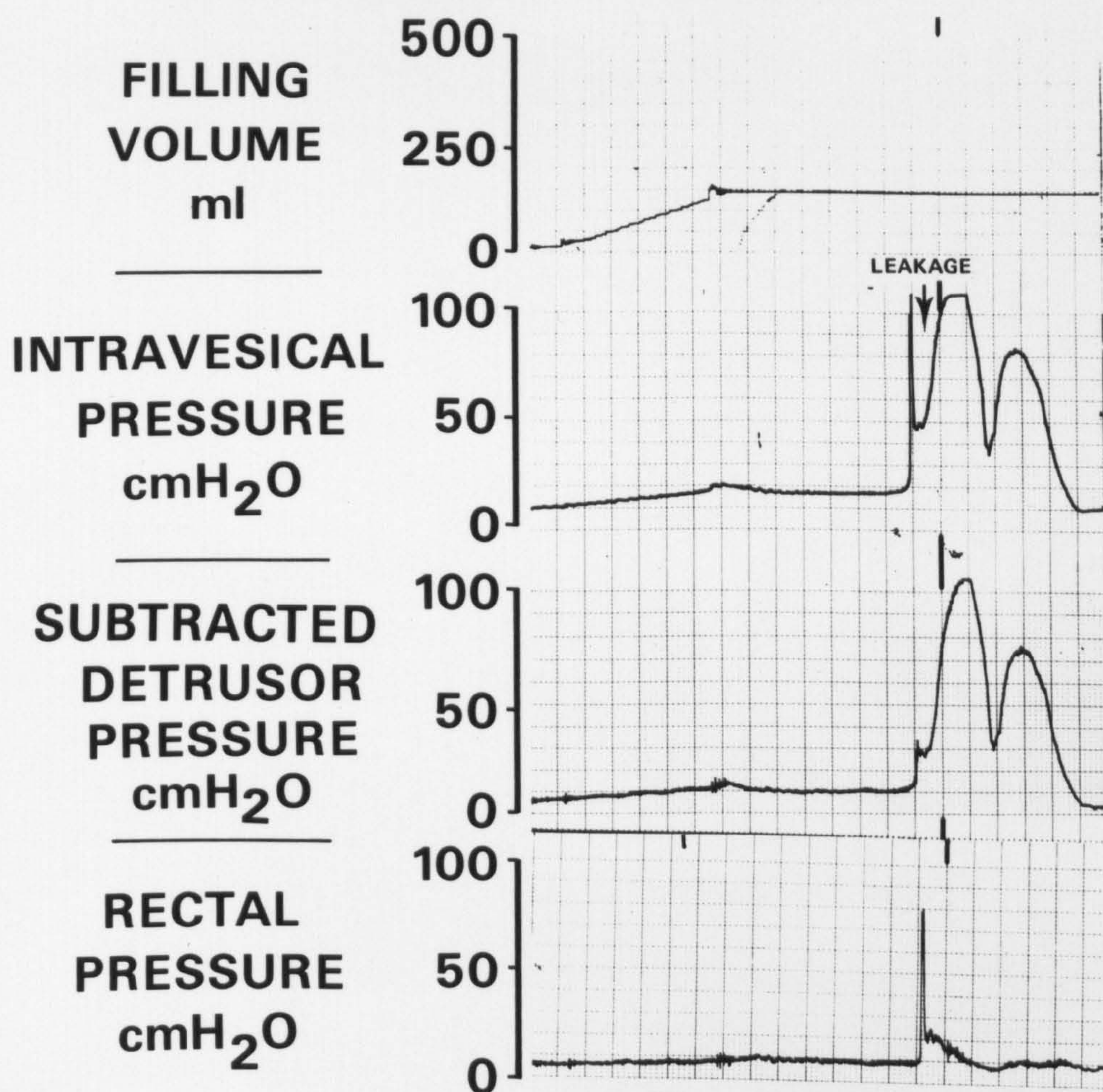


FIGURE 3D - Detrusor Instability : Cough Provoked.



FIGURE 3E - Video Record of Synchronous Pressure Flow

Cystourethrography showing Grade 2 Genuine Stress

Incontinence (i.e. with leakage of contrast medium).

3.3 URETHRAL PRESSURE PROFILOMETRY

The details of the technique are listed below
(based on ICS Standardisation Committee 1976 recommendations).

Catheter type and size: Plastic, 8 French gauge.
1 side hole 5 cm from tip.

Measurement technique: Brown and Wickham.

Rate of infusion: Saline at 2 ml per minute.
(Braun-Melsungen perfusion pump).

Continuous or inter-
mittent withdrawal: Continuous.

Rate of Withdrawal: 0.25 cm per second.

Bladder Volume: Zero.

Position of patients: Supine.

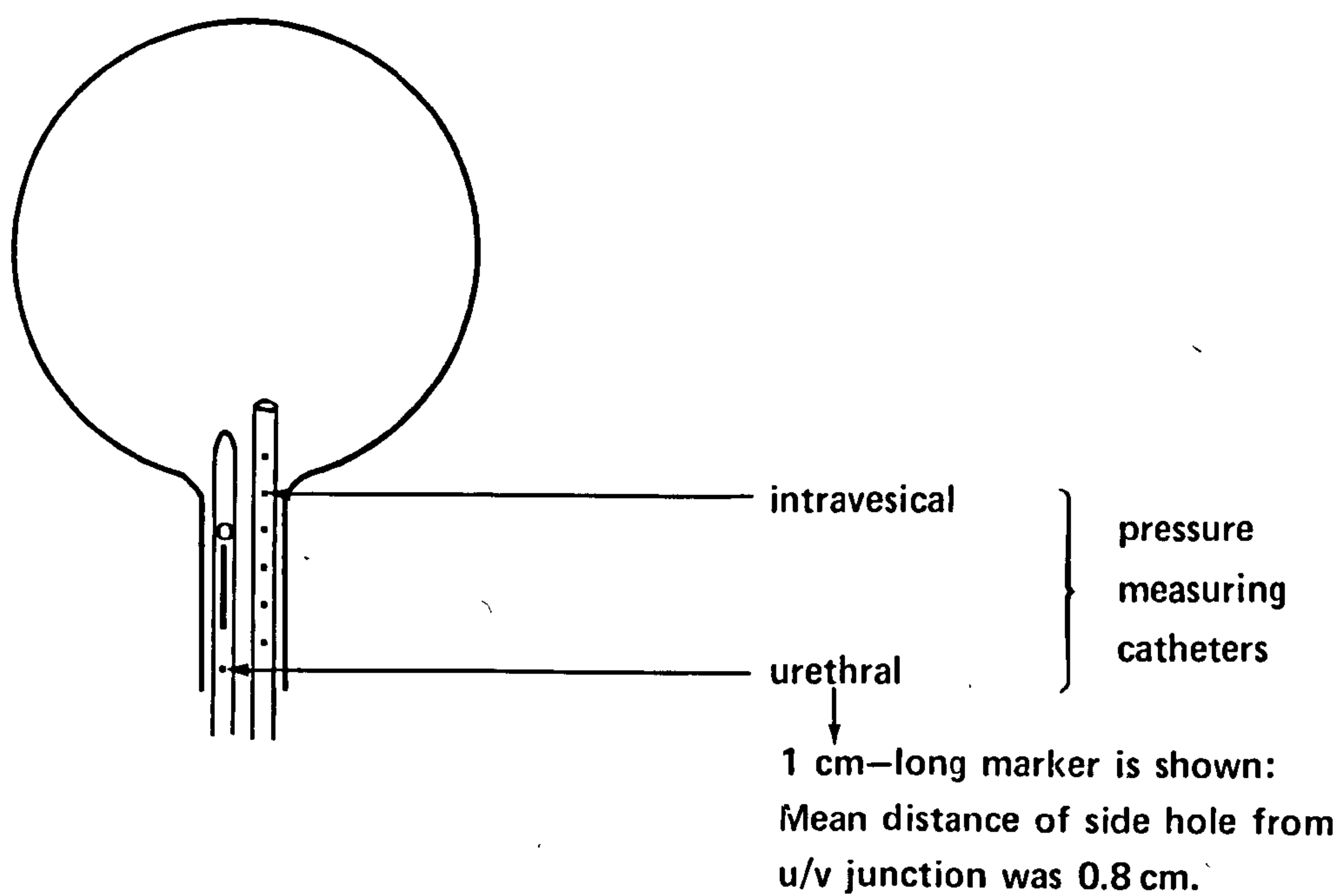
3.4 FLUID BRIDGE TEST (FBT)

The same apparatus and technique was used as described for synchronous video pressure flow cystourethrography. When maximum bladder capacity on erect filling cystometry had been reached and the filling catheter had been removed (leaving the intra-vesical pressure measuring cannula in situ), the screening table was returned to the supine position. An infant feeding tube (1.65 mm external diameter) was then inserted to measure urethral pressure changes and there was a 1 cm long radio-opaque marker immediately proximal to the 2 side holes both of which were 1 cm from the tip (Figure 3F).

The urethrovesical junction was located by withdrawing the urethral catheter from the bladder until a pressure rise was noted and the catheter was then positioned so that the urethral pressure recording side holes were between 0.5 - 1 cm from the internal urethral meatus. The position was checked by radiological screening and the distance of the catheter's holes from the U.V. junction was measured using the marker as a guide (Figure 3G).

The urethral catheter perfusion rate was then reduced and with the polygraph recording at a paper speed of 5 cm per second, the patient coughed once and bladder and urethral pressure changes were measured. In each patient the test was repeated two or three times in the supine position. The screening table was then tilted to the erect position and the new distance of the urethral catheter

DIAGRAM SHOWING CATHETER POSITIONS DURING FBT

FIGURE 3F

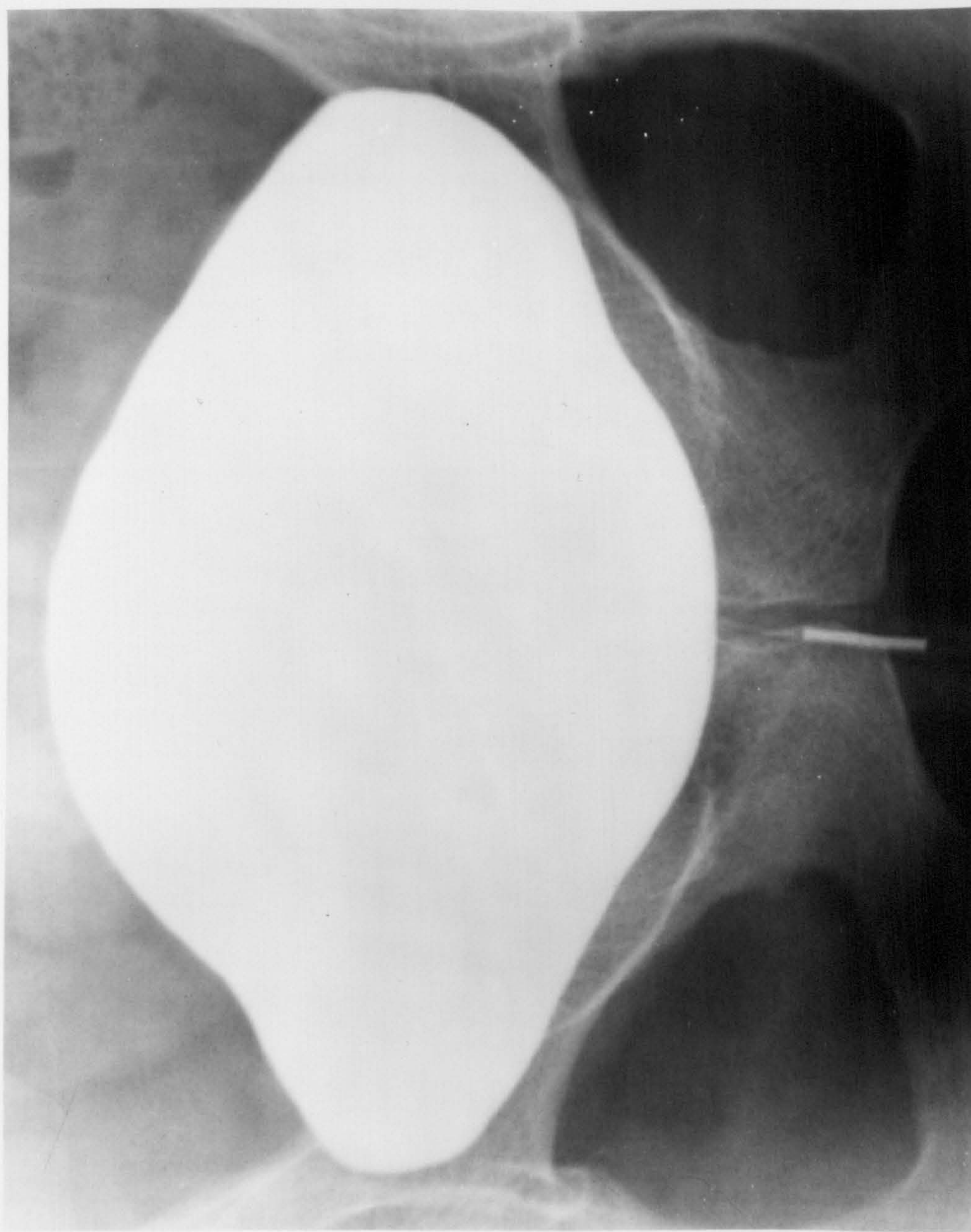


FIGURE 3G - Cystourethrogram showing the Urethral Catheter with marker in position during the F.B.T. (Supine).

side holes from the U.V. junction was measured as previously. The test was then repeated in the erect position. A positive FBT (Figure 1G) was indicated by simultaneous bladder and urethral pressure increases following a cough (i.e. a fluid bridge had occurred due to opening of the proximal urethra) and a negative test (Figure 1H) was denoted by a lack of urethral pressure changes.

3.5 URILOS NAPPY TEST

Each patient was instructed to wear the nappy (inserted between her vulva and panties) at home for two hours and carry out her normal routine. On arrival at Hospital the nappy was connected to the meter and the urine lost measured.

A possible error with this method is evaporated urine loss. The accuracy of this method was assessed by measuring the reproducibility between several nappies in the same and different packs and by measuring evaporation from them in Chapter 5.

CHAPTER 4

ASPECTS OF DIAGNOSIS

OF GENUINE STRESS INCONTINENCE

4.1 INTRODUCTION

The diagnosis of genuine stress incontinence is based on the identification of urethral incompetence in the absence of detrusor instability. The latter is usually excluded by cystometry (1.3.6) while urethral incompetence is commonly detected by cystourethrography (1.3.7), but more recently by the Fluid Bridge Test (1.3.10). Two studies were carried out to examine both these aspects of the diagnosis of genuine stress incontinence.

4.2 POSTURAL CYSTOMETRY AND THE EFFECT OF AGE IN DETECTING DETRUSOR INSTABILITY

A retrospective study was carried out to assess the value of the "provocative tests" described in the last Chapter in detecting detrusor instability and to evaluate postural cystometry and the effect of age.

4.2.1 Patients and Methods

The cystometrograms of 316 consecutively investigated women were studied retrospectively. The ages ranged from 9 to 93 (mean 55) years and none had outflow obstruction or neurological disease. Synchronous video pressure flow cystourethrography had been performed and the stability of the detrusor muscle had been assessed by the six "provocative tests", (3.2.2). The contribution of these tests, in particular the effect of posture, in provoking detrusor instability was then estimated. This was also assessed in relation to the age of the patient.

4.2.2 Results

141 of the 316 patients studied (44.6%) had unstable bladders (including 30 women with combined detrusor instability and genuine stress incontinence). The remaining 175 had stable detrusors with genuine stress incontinence. The contribution of each of the "provocative tests" in demonstrating detrusor instability is shown in Figure 4A. 86 (61%) bladders contracted on

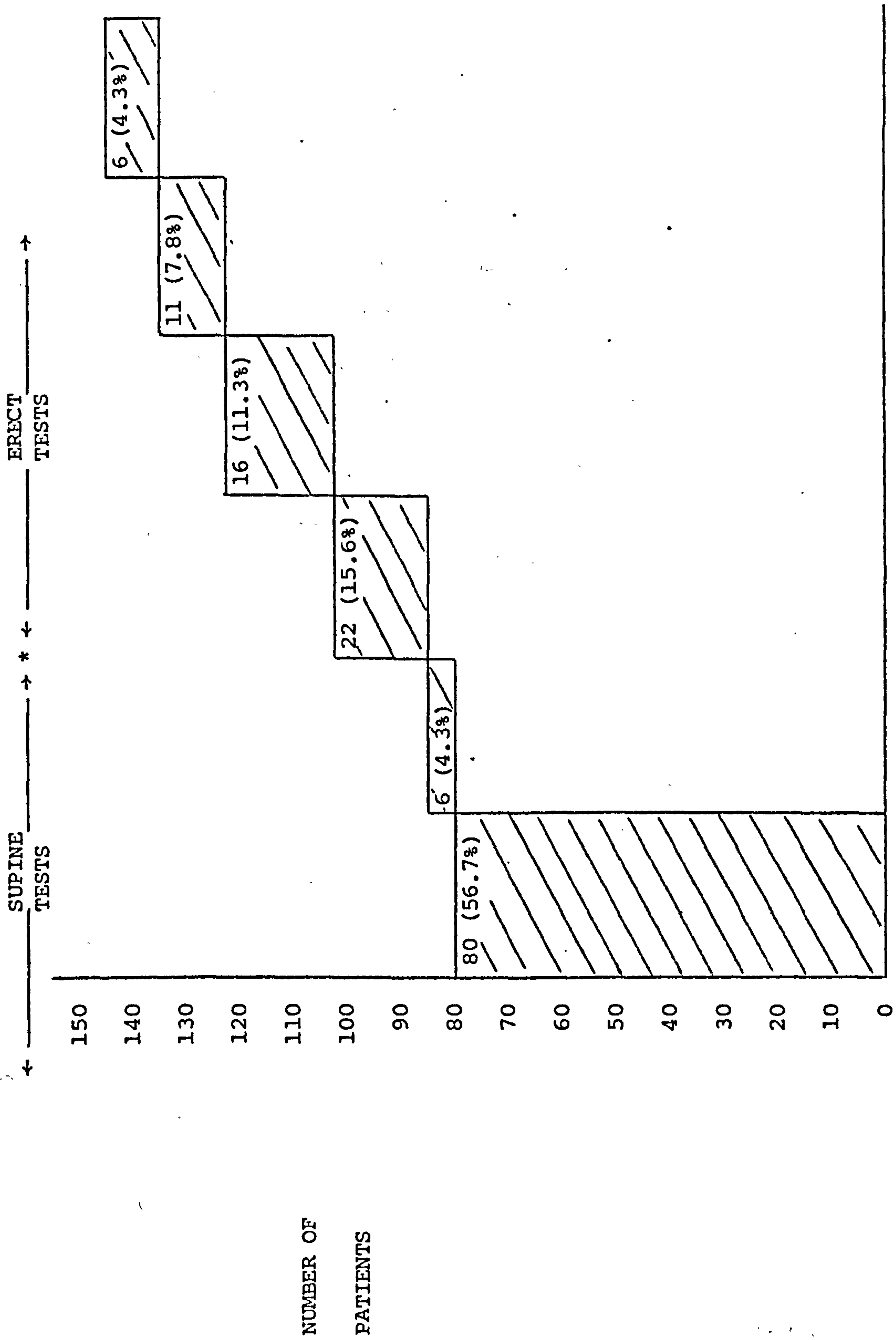


FIGURE 4A INITIAL AND SUBSEQUENT TESTS PROVOKING UNINHIBITED DETRUSOR CONTRACTIONS IN 141

UNSTABLE BLADDERS

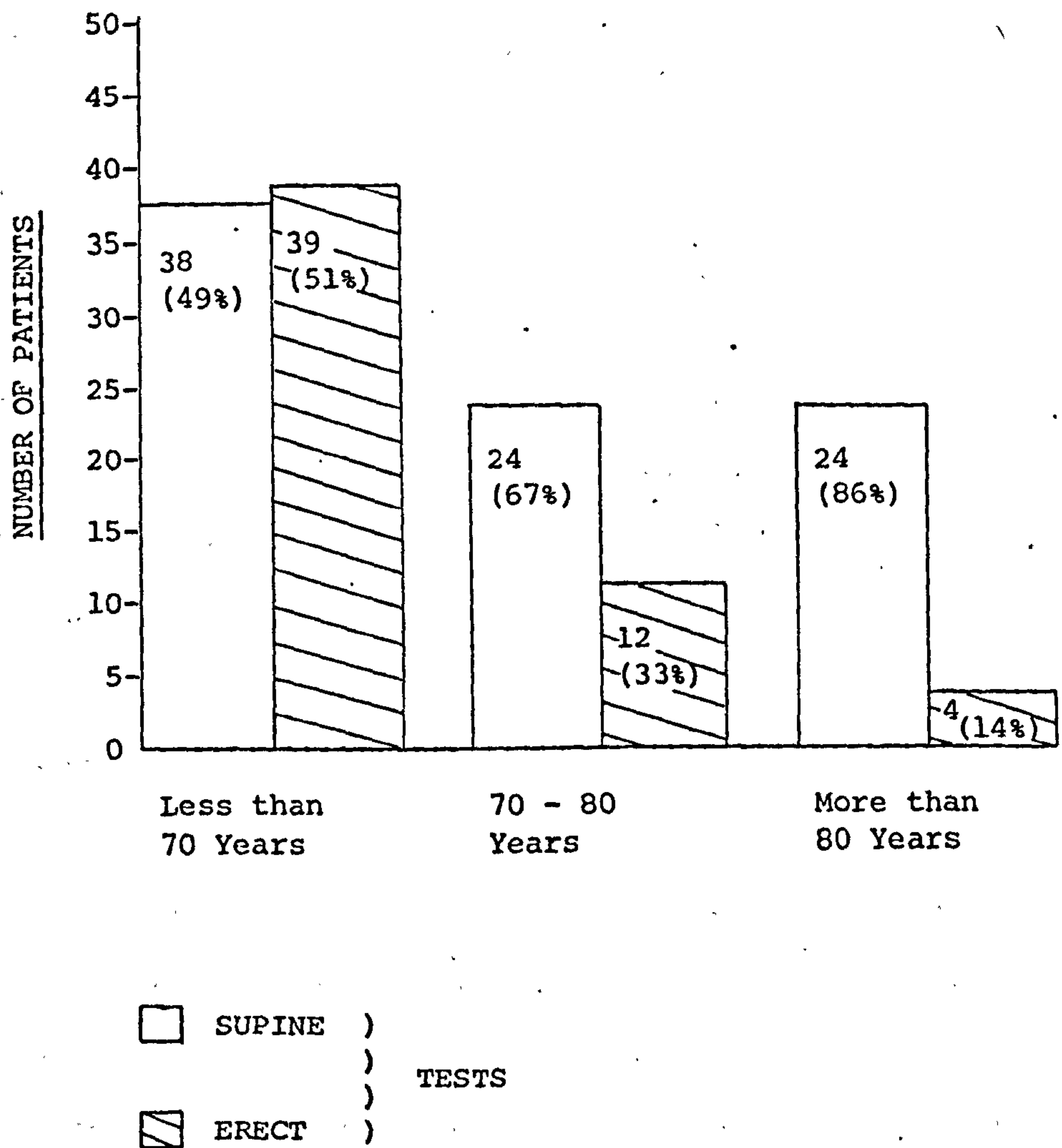


FIGURE 4B

POSTURAL CYSTOMETRY AND THE EFFECT
OF AGE IN DETECTING DETRUSOR INSTABILITY

supine testing while 55 (39%) required erect provocation to demonstrate the abnormality. The mean ages of the "supine provoked" patients and those requiring erect testing were 66 and 57 years respectively, and this age difference was statistically significant ($p < 0.01$ Students t test).

The age distribution of these 2 groups is presented in Figure 4B. Just over 50% of those patients aged under 70 years required erect testing to demonstrate detrusor instability in comparison to 14.3% (4 out of 28) of those patients aged over 80 years.

4.2.3 Discussion

The results of this study confirm Arnolds (1974) work of the importance of studying postural influences on cystometry in the diagnosis of detrusor instability; 50% of the patients in a non-geriatric population with unstable bladders would have remained undetected if supine tests only had been performed compared with Arnold's finding of 58% (ages were not given in his study).

In addition, this postural effect has been shown to be related to the age of the patient; as age increased, supine cystometry detected a higher proportion of cases of detrusor instability with only four of the twenty-eight (14.3%) patients over 80 years requiring erect tests. This phenomenon may be related to the different aetiology of detrusor instability with advancing age and a neuropathic basis due to cerebral atherosclerosis and

senescence becomes more common. However it remains important to study postural influences on cystometry at all ages if detrusor instability is not to go undiagnosed in those whose supine cystometry is normal.

4.3 AN ASSESSMENT OF THE ACCURACY OF THE FLUID BRIDGE TEST COMPARED WITH CYSTOURETHROGRAPHY IN THE DIAGNOSIS OF GENUINE STRESS INCONTINENCE

A study was carried out to compare the above two methods described in the previous Chapter of detecting urethral incompetence.

4.3.1 Patients and Methods

30 incontinent patients aged between 22 and 69 years were studied. Synchronous video pressure flow cystourethrography was carried out (3.2.) and all the patients had stable detrusor function. At maximim bladder capacity in the erect position, cough leakage of contrast medium and opening of the proximal urethra was noted.

Immediately following this the Fluid Bridge Test was performed supine (3.4) and in 21 patients it was repeated in the erect position. The Fluid Bridge pressure profiles were compared with the cystourethrographic appearances.

4.3.2 Results

The results are summarised in Table 4A. The mean distance of the urethral catheter side holes from the urethral vesical junction was 0.8 cm. The urethral catheter did not move during the Fluid Bridge Test but

CYSTOURETHROGRAPHY	FLUID BRIDGE TEST	
Cough Leakage	Fluid Bridge Occurred	
Present (+)	Yes (+)	
Absent (-)	No (-)	
Equivocal (E)		
ERECT	SUPINE	ERECT
(30 patients)	(30 patients)	(21 patients)
15 +	7 + 8 -	9 + 3 -
12 -	1 + 11 -	7 -
3 E	3 +	2 +

TABLE 4A

COMPARISON OF CYSTOURETHROGRAPHY WITH
THE FLUID BRIDGE TEST

in approximately 60% of measurements it did so during posture change.

On erect cystourethrography 15 of the 30 patients had cough leakage; 7 of these had a positive supine FBT and of the 12 patients undergoing erect testing, 9 had a positive FBT.

11 women had no cough leakage on cystourethrography and a negative FBT. Of the remaining 4 patients who had a positive FBT with equivocal (3) or no (1) cough leakage on x-ray, 3 had marked bladder base prolapse which obscured the view of the urethra.

4.3.3 Discussion

In the comparison of two tests, the ideal is to have an accurate "yardstick" against which the two tests can be set. Unfortunately no such yardstick exists in the diagnosis of genuine stress incontinence. Therefore in this study, the accuracy of the newer Fluid Bridge Test was compared against the more traditional test of cystourethrography with emphasis being placed on the visualisation of cough leakage of contrast medium as this is unequivocal evidence of urethral incompetence. Equally, the analysis could have been carried out the other way round, with cystourethrography being compared against the FBT. However accepting these deficiencies, although the Fluid Bridge Test produced better correlation with cystourethrography in the erect rather than supine position,

it was less reliable than cystourethrography in the diagnosis of genuine stress incontinence as it was associated with 25% false negative results (3 cases out of 12). This is similar to the 28.5% "false negative" incidence noted by Sutherst and Brown (1980a) in their evaluation of the test. Another major problem of the FBT was positioning the urethral catheter in relation to the urethro-vesical junction which was aggravated further by posture changes when catheter movement occurred in about 60% of occasions. The advantages of this test are that it is relatively inexpensive to perform, its interpretation is simple and it is helpful when bladder base prolapse obscures urethral changes.

The advantages of cystourethrography are that it is a comprehensive test because it will usually reveal bladder neck opening with/without leakage and also it may show ureteric reflux, diverticula and outlet obstruction. It can also be easily combined with cystometry. The disadvantages of cystourethrography include the radiation risk; with an average screening time of 1 - 2 minutes the patient dose is slightly less than that received from a full intravenous urogram (12,000 M.R.) (Bates and Corey, 1971).

Overall, combined provocative cystometry and cystourethrography is still the most valuable test available to diagnose genuine stress incontinence. A major theoretical disadvantage of this is the equipment cost. Arnold et al (1974) calculated that the equipment necessary would be in the region of £4,000. Today it

is probably over £10,000 for the urodynamic equipment assuming a suitable x-ray room with image intensifier and tilting table is already available. It requires the skills of a Radiologist or trained Radiographer as well as a nurse, technician and a Doctor with a good understanding of urodynamics for the maximum amount of information to be obtained. Thus this technique must be limited to specialist centres.

CHAPTER 5

AN ASSESSMENT OF THE URILOS SYSTEM

5.1 INTRODUCTION

The Urilos System was designed to quantify urine loss by an incontinent patient (1.3.11). Previous technical and clinical evaluations have been described by Rowan et al (1976) and Stanton and Ritchie (1977), however their numbers were small; they observed that using a measured quantity of urine, the difference between 2 nappies was 13% (Stanton and Ritchie) and between 2 packs of nappies was 17% (Rowan et al). Their clinical assessment consisted of the patient attending with a comfortably full bladder and wearing a nappy which was attached to the meter by a variable length of lead. Several manoeuvres were performed to reproduce the conditions causing incontinence. However this method has the disadvantage of the artificial hospital environment and the limitations imposed by the length of lead. The Urilos Nappy Test used in the conservative treatment studies has been described in Chapter 3. It consists of the patient wearing the nappy at home for 2 hours, carrying out her normal routine and on arrival at hospital, the nappy is connected to the meter and the urine loss measured. A possible error with this method is evaporated urine loss. The accuracy of this method was assessed by measuring the reproducibility between several nappies in the same indifferent packs and by measuring evaporation from them.

5.2 PATIENTS AND METHOD

5.2.1 Nappy Reproducibility within the same and between different packs

5 nappies were randomly selected from each of 4 packs of 25 (supplied by N.H. Eastwood and Son Limited) so that 20 pads were tested. 5 ml of urine was poured onto the centre of each pad at 2 minute intervals until 100 mls had been applied. The meter reading was recorded after 1 minute on each occasion. The results were compared between nappies in the same and different packs.

5.2.2 Evaporated Urine Loss

Since it is aesthetically unsatisfactory for women to wear urine soaked pads for several hours, evaporation of urine and Ringer's lactate* solution was compared. 20 ml of urine and Ringer's solution were added to 2 nappies from the same pack. Meter readings were taken at 30 minute intervals for four hours. The evaporation loss from both nappies was similar (Figure 5A).

10 normal women each wore a nappy soaked with 20 ml of lactate solution for 3 hours and continued their normal activities. Meter readings were recorded initially and every half hour thereafter. The evaporation loss was calculated.

*Composition: Sodium 147 millimoles per litre; potassium 4 millimoles per litre; calcium 2 millimoles per litre; chloride 155 millimoles per litre.

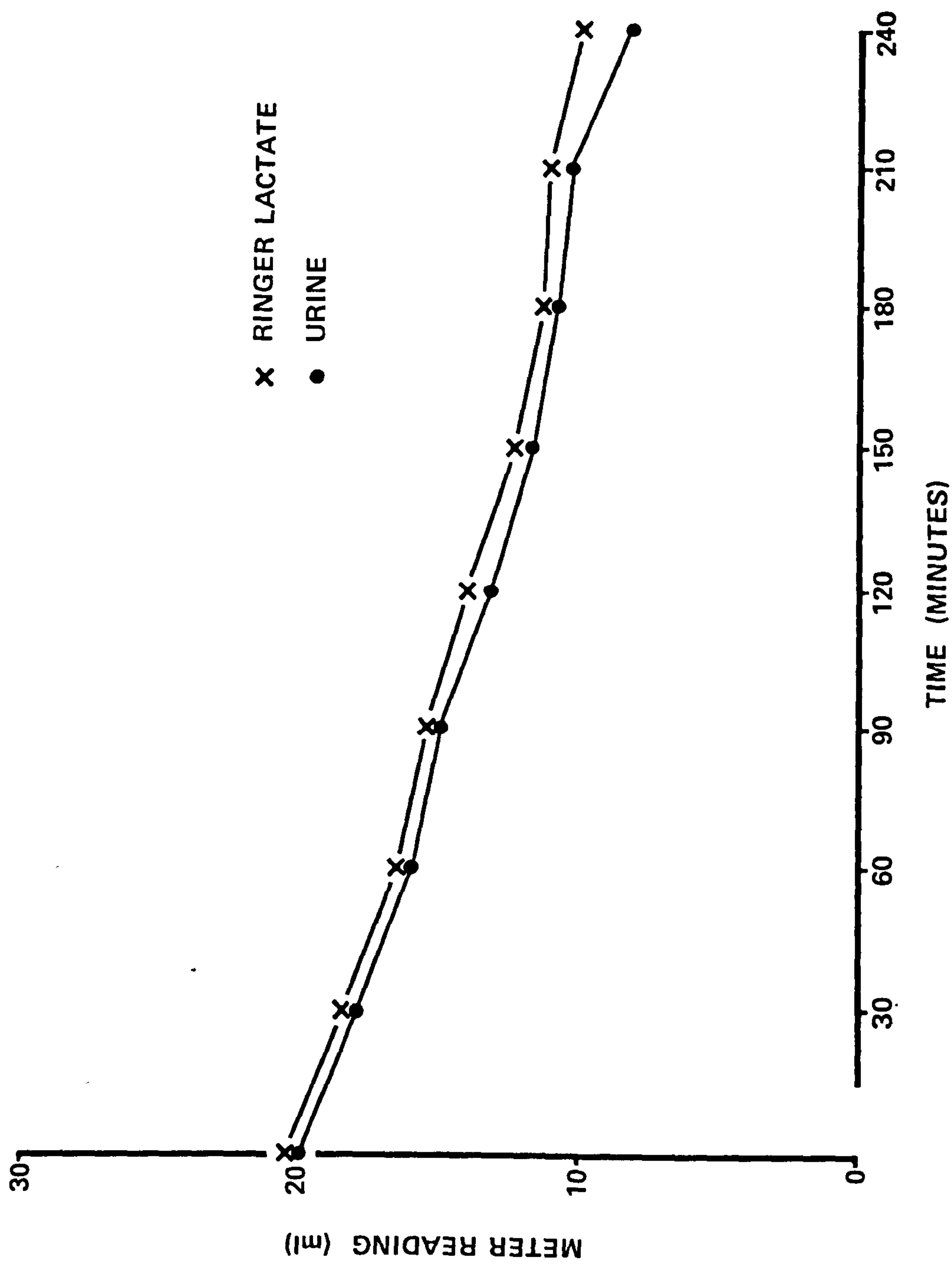


FIGURE 5A - Evaporation from 2 nappies each containing 20 ml of urine or Ringer's Lactate Solution.

5.3 RESULTS

5.3.1 Nappy Reproducibility

Table 5A shows the mean readings of the successive 5 ml increments (\pm SD) for each nappy and the mean increments and percentage errors for each pack. The relatively large standard deviation for each nappy shows that there is considerable variation to the 5 ml increments particularly in packs 2 and 4. There was approximate correlation between nappies in the same pack; however, a consistent under-recording with a mean error of about 25 per cent was found in packs 1 and 3, and there was over-recording with a mean error of 21 and 23 per cent in packs 2 and 4 respectively. A comparison between packs showed that after 50 ml of urine had been applied to the nappies there was a difference in the mean recordings of up to 34 ml (68 per cent, between packs 3 and 4), (Figure 5B). After the first 5 ml application one nappy failed to register while 19 recorded a mean value of 4.2 ml.

5.3.2 Evaporated Urine Loss

Table 5B shows the evaporation from 10 nappies (from pack 2) each containing 20 mls of lactate solution. The mean initial reading after fluid addition was 24.3 ml (an error of 21.5%); evaporation loss was 7.8 and 19.8 at 90 and 180 minutes respectively.

<u>PACKS</u>				
	1	2	3	4
Mean of 5 ml increments (\pm SD) for each nappy (ml).	3.9 \pm 1.1	6.3 \pm 1.5	4.1 \pm 0.9	6.3 \pm 2.7
	3.6 \pm 0.8	5.9 \pm 2.0	3.2 \pm 0.7	5.9 \pm 2.4
	3.6 \pm 1.1	6.3 \pm 1.9	3.8 \pm 0.7	6.3 \pm 2.7
	4.2 \pm 1.3	6.3 \pm 2.1	3.9 \pm 0.7	6.3 \pm 3.1
	3.5 \pm 2.1	5.6 \pm 1.9	3.9 \pm 0.8	6.2 \pm 2.2
Mean of 5 ml increments (\pm SD) for each pack of nappies (ml).	3.7 \pm 0.3	6.1 \pm 0.3	3.8 \pm 0.3	6.2 \pm 0.2
Mean percentage error (\pm SD) for each pack of nappies	-25.4 \pm 5.8	+21.2 \pm 5.7	-25.0 \pm 6.7	+23.3 \pm 3.2

TABLE 5A

NAPPY REPRODUCIBILITY WITHIN THE SAME AND BETWEEN DIFFERENT PACKS

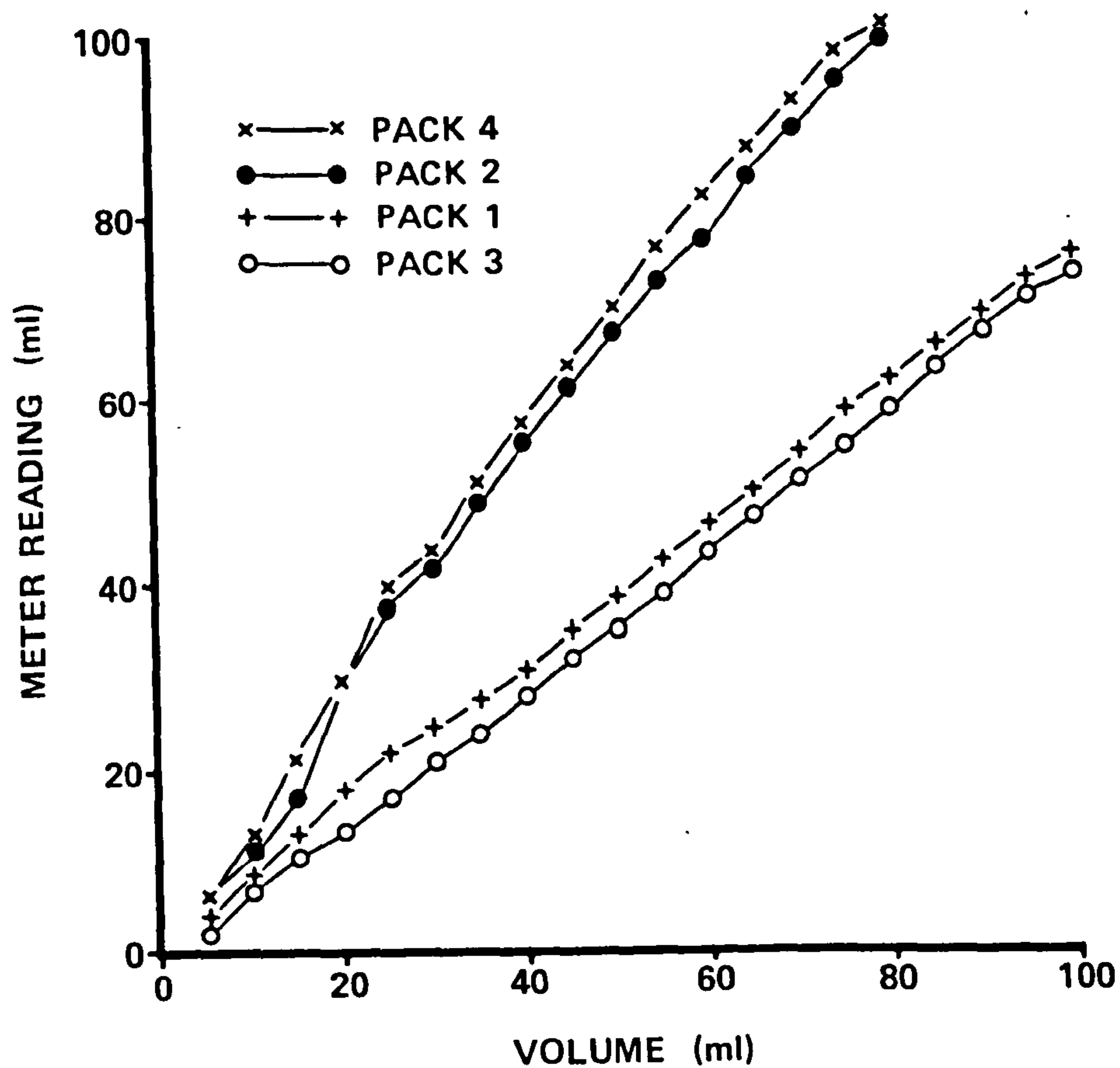


FIGURE 5B - Mean meter readings against total urine volumes added to nappies from four packs.

Mean Reading Initially and at 30 minute intervals thereafter		Loss Due to Evaporation Based on Initial Reading (per cent)
<u>TIME (Minutes)</u>	<u>ML</u>	
0	24.3	
30	23.2	4.1
60	23.1	4.9
90	22.4	7.8
120	20.9	14.0
150	20.2	16.8
180	19.5	19.8

TABLE 5B

EVAPORATION FROM TEN NAPPIES EACH CONTAINING
20 ML OF RINGER'S LACTATE SOLUTION

5.4 DISCUSSION

The data shows an approximate reproducibility of urine loss measurements between nappies in the same pack but there were under- and over-recordings of up to 25 and 23 per cent respectively; Stanton and Ritchie (1977) observed a difference of 13 per cent between two nappies. When packs were compared differences were up to 68%; this result compared adversely with Rowan et al (1976) who found an error of 17%. Nineteen of the twenty nappies registered approximately the initial 5 ml of urine, therefore, the majority of pads will confirm minimal incontinence. However, while the Uriilos System is an excellent concept in principle, because of the major problems of under- or over-recordings between nappies and poor reproducibility between packs or nappies, it is not as yet, a sufficiently reliable method of quantifying incontinence.

An 8% urine evaporation loss over 90 minutes is acceptable while the 20% loss in three hours invalidates results. The nappy's use for 60 - 90 minutes in the patient's home before attending hospital has the advantages that she may reproduce more exactly the conditions provoking incontinence and there is time-saving of clinical or technical personnel.

In the conservative treatment studies (Chapter 6 and 8) the evaporation loss was not relevant since this was the same before and after treatment as the same conditions prevailed, i.e. same length of time nappy worn, same time

of day and same season of year. However, each patient was given nappies from the same pack before and after treatment to avoid the errors of pack differences.

CHAPTER 6

THE VALUE OF PHYSIOTHERAPY IN THE

TREATMENT OF GENUINE STRESS INCONTINENCE

6.1 INTRODUCTION

There has been no objective assessment of the use of physiotherapy in genuine stress incontinence, nor a comparison of different methods of muscle stimulation used as an adjunct to pelvic floor exercises (1.4.7). A prospective study was therefore carried out in genuine stress incontinent patients which had the following aims:

1. To assess objectively the value of physiotherapy.
2. To compare pelvic floor exercises with/without faradism or interferential therapy.
3. To identify the factors contributing to the success or failure of these treatments.

6.2 PATIENTS AND METHODS

6.2.1 Patients and Study Design

Sixty patients aged 19 - 79 mean (46.8) years were studied. They all had had an independent flow rate (1.3.4) and synchronous video pressure flow cystourethrography carried out (3.2), and been shown to have stable detrusor function with no outlet obstruction and been diagnosed to have genuine stress incontinence. In 20 patients the Fluid Bridge Test (3.4) was also performed. Twelve of the women had undergone previous incontinence correcting surgery. The patients were divided randomly into four groups and they received the following treatment:

- | | | |
|---------|---|---------------------------|
| Group 1 | - Pelvic Floor Exercises |) In the Physiotherapy |
| | (PFE) alone. |) Department for 12 |
| Group 2 | - PFE + faradism. |) sessions in 6 weeks. |
| Group 3 | - PFE + interferential |) Also an instruction |
| | therapy. |) sheet describing pelvic |
| | | muscle exercises to be |
| | | performed daily at home |
| | | for 6 weeks. |
| Group 4 | - PFE in the Physiotherapy Department for 1 | |
| | session only and also the above instruction | |
| | sheet. | |

A description of the physiotherapy techniques employed is as follows:-

6.2.2 Pelvic Floor Exercises

These were designed to strengthen the urethral and periurethral striated muscles. The patient instruction sheet for home pelvic exercises is shown in Figure 6A. A perineometer similar to that devised by Kegel (1948) was used during the exercises in the Physiotherapy Department to enable the patients to be aware of the pelvic floor muscles to contract. It consisted of a compressible silicone rubber air chamber, 8 cm long x 3 cm in diameter connected by plastic tubing to a manometer (Figure 6B). (A smaller air chamber 1.5 cm in diameter was also available for older patients with vaginal atrophy and narrowing). The base of the air chamber was expanded so that it rested against the perineum so limiting its position in the vagina. As the appropriate muscles contracted the manometer registered any increase of air pressure within the chamber. The patients were instructed to "hold" each contraction for approximately 5 seconds and then rest for 15 seconds between each contraction to avoid fatigue. Each treatment session consisted of 3 groups of 6 contractions with a 2 minute rest period between each group.

As well as affording a visual guide of muscle contraction the perineometer readings recorded at the beginning and end of treatment were noted for each patient to assess response to treatment.

PELVIC FLOOR EXERCISES

Lie down and relax completely. When you feel relaxed tighten the muscles that stop you passing urine, making sure that your other muscles are relaxed. Hold the contraction for a few seconds then relax completely.

Try to practice this exercise very regularly. At first you will have to lie down or sit to make sure that your muscles are quite relaxed but later you may be able to practice while standing. Try to practice five times before you get up, five times once you are up and five times every half hour thereafter. As you feel the contractions getting stronger you can increase them to ten times every half hour.

Try several times to stop and start the stream when you are passing water. You may find this exercise difficult at first but with practice you will be able to control the stream more easily. Again, when you are exercising these muscles, the rest of you must be relaxed completely.

FIGURE 6A

PATIENTS' INSTRUCTION SHEET FOR HOME PELVIC FLOOR EXERCISES

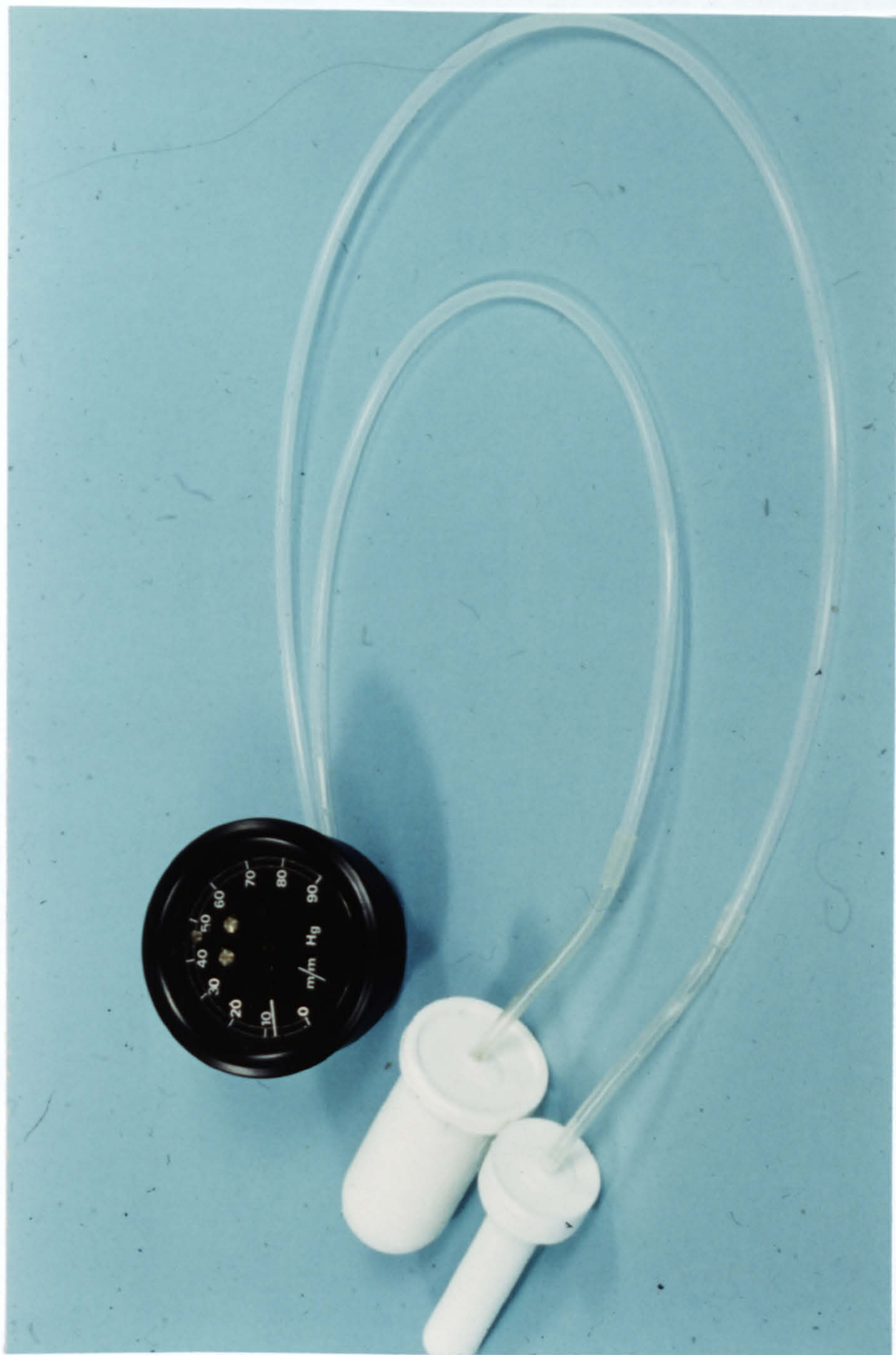


FIGURE 6B - Perineometers.

6.2.3 Faradism

The patient sat with her back supported. The indifferent electrode, covered with damp lint, was saddle shaped similar to that described by Scott et al (1969) and it was placed over the patient's sacrum. The active button electrode also covered with lint, was placed in the perineum.

A Minidyn Faradic Battery was used and surges of approximately 2 seconds duration at a repetition rate of 12 surges per minute were given using a current as strong as the patient could tolerate comfortably. The patient was asked to aid contraction of her pelvic floor muscles when the current was felt so that later she would be able to practice muscle contraction without the faradic stimulus. Each treatment session consisted of three groups of twelve contractions with a 2 minute rest period between each group.

6.2.4 Interferential Therapy

The regime described by McQuire (1975) was used. Four medium vacuum suction electrodes (two each on the abdomen and the adductor muscles of the thighs) transmitted a 20 - 25 milliamperes current which gave 15 pulses at pressure peak 0.25 to 0.30 kilo pascals per cm^2 (mostly 0.3 kP/cm^2). The first treatment lasted 10 minutes. The patient was instructed to relax while the pelvic floor muscles were stimulated and if there were no ill effects after the first session the duration was increased to 15 minutes for the second and subsequent (total of twelve) courses.

After each session (both faradism and interferential therapy) the pelvic floor exercises were practised using the perineometer.

6.2.5 Patient Assessment

Subjective assessment was carried out at 6 weeks and 6 months when the patients were asked if they were much improved, improved or no better.

Before and after each 6 week course of treatment the following objective assessments were carried out.

1. A 7 day bladder chart (1.3.2), (Each patient also completed a 7 day bladder chart at the 6 month assessment).
2. Perineometer measurements.
3. A urethral pressure profile by the method of Brown and Wickham (3.3), which was also repeated during pelvic floor muscle contractions.
4. Urilos Nappy Test measuring urine loss over 2 hours of normal activity (3.5).

6.2.6 Statistical Analysis

60 patients were studied and were randomly allocated into 4 groups as mentioned previously. The value of physiotherapy was assessed in the 45 patients receiving active Hospital based treatment (Groups 1, 2, and 3). Each patient acted as her own control and a subjective and objective assessment as performed before and after treatment and a comparison made using the paired Student t Test*. A subjective and objective comparison of the 4 methods of physiotherapy was performed using a standard analysis of variance*. The patients receiving Hospital based treatment (Groups 1, 2 and 3) were divided into "successes" (those who were much improved) and "failures" (those who were no better) and these were compared to identify the contributing factors by the 2 sample Student t Test and the Fisher Exact Test*.

*See Appendix.

6.3 RESULTS

6.3.1 The Value of Physiotherapy

Subjective Assessment

Of the 45 patients undergoing Hospital based physiotherapy (Group 1: PFE, Group 2: PFE + faradism, Group 3: PFE + interferential therapy) 13 felt they were no better, 15 felt they were improved, and 17 much improved on completion of their 6 week treatment course. At 6 months after treatment, 16 and 12 of the 44 patients assessed felt they were still "improved" and "much improved" respectively. (Table 6A).

Objective Assessment

The results of the objective parameters examined before the after treatment (at 6 weeks) of the 45 patients receiving Hospital based physiotherapy are summarised in Table 6B. There was a highly significant reduction in pad changes per 24 hours (2.5 pads before, 1.3 pads after treatment $p < 0.0005$) and a highly significant increase in perineometer readings (6.0 mm Hg before, 13.8 mm Hg after treatment $p < 0.0005$). There were also significant reductions in the Urilos Nappy Test (3.3 ccs/2 hours before, 1.7 ccs/2 hours after, $p < 0.005$) and in urinations per 24 hours (8.9 before, 7.9 after, $p < 0.0025$). The urethral pressure profiles increased significantly both measured at rest (52.6 cms H_2O before, 56.5 cms H_2O after, $p < 0.005$) and during pelvic floor muscle contraction (60.0 cms H_2O before, 64.3 cms H_2O after, $p < 0.01$).

At 6 months after treatment the mean pad changes were 1.5 pads per 24 hours and this was still significantly reduced from the initial 2.5 pads per 24 hours, ($p < 0.005$).

	<u>Six Week Assessment</u>			<u>Six Month Assessment</u>		
	No Better	Improved	Much Improved	No Better	Improved	Much Improved
Patient Numbers	13	15	17	16 *	16	12
Total	45			44*		

* One patient did not attend for assessment.

TABLE 6A

SUBJECTIVE ASSESSMENT AT SIX WEEKS AND SIX MONTHS
OF 45 PATIENTS RECEIVING HOSPITAL BASED PHYSIOTHERAPY
(GROUPS 1, 2 AND 3)

Parameter (number)	Before Treatment (Mean \pm SD)	After Treatment	t Value	Statistical Significance
Urinations/24 hr (45)	8.9 \pm 2.8	7.9 \pm 1.9	3.02152	p < 0.0025
Pad changes/24 hr (45)	2.5 \pm 2.2	1.3 \pm 1.8	5.7189	p < 0.0005
Perineometry Reading (mm Hg) (45)	6.0 \pm 4.5	13.8 \pm 8.9	6.8375	p < 0.0005
Maximum urethral closure pressure (cms H ₂ O) (35)	52.6 \pm 16.8	56.5 \pm 16.5	2.7916	p < 0.005
Maximum urethral closure pressure + pelvic floor contraction (cm H ₂ O) (35)	60.0 \pm 17.1	64.3 \pm 16.6	2.4774	p < 0.01
Urilos (Urine lost in cc/2 hours) (25)	3.3 \pm 6.1	1.7 \pm 5.2	3.0194	p < 0.005

TABLE 6B

**OBJECTIVE ASSESSMENT OF 45 PATIENTS RECEIVING HOSPITAL
BASED PHYSIOTHERAPY (GROUPS 1, 2 AND 3)**

GROUP 1
(PFE in Hospital)
n = 15

GROUP 2
(PFE & Faradism)
n = 15

GROUP 3
(PFE & Interferent-
ial Therapy)
n = 15

GROUP 4
(PFE at home)
n = 15

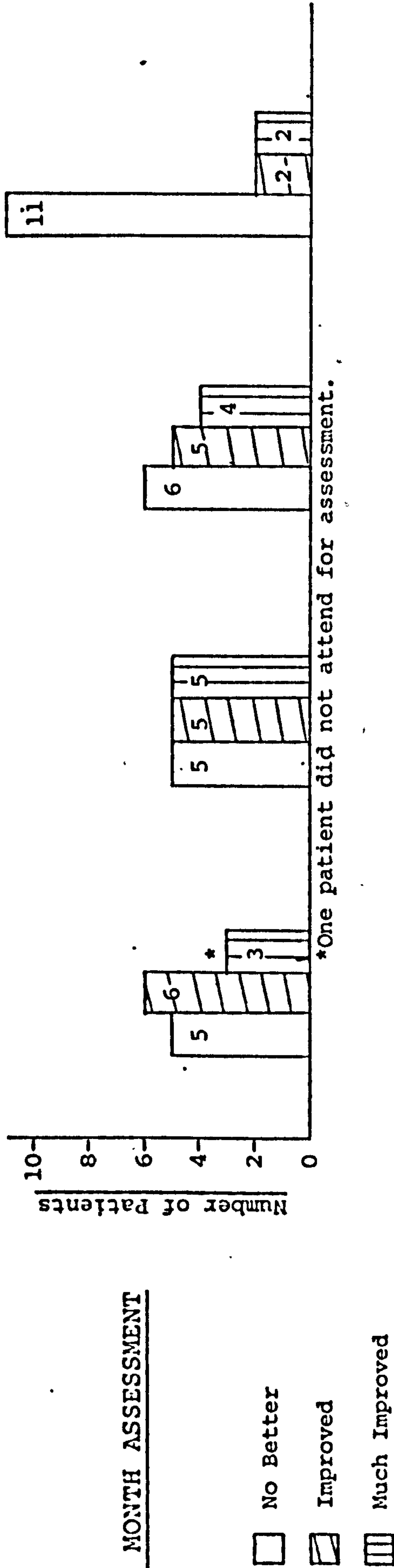
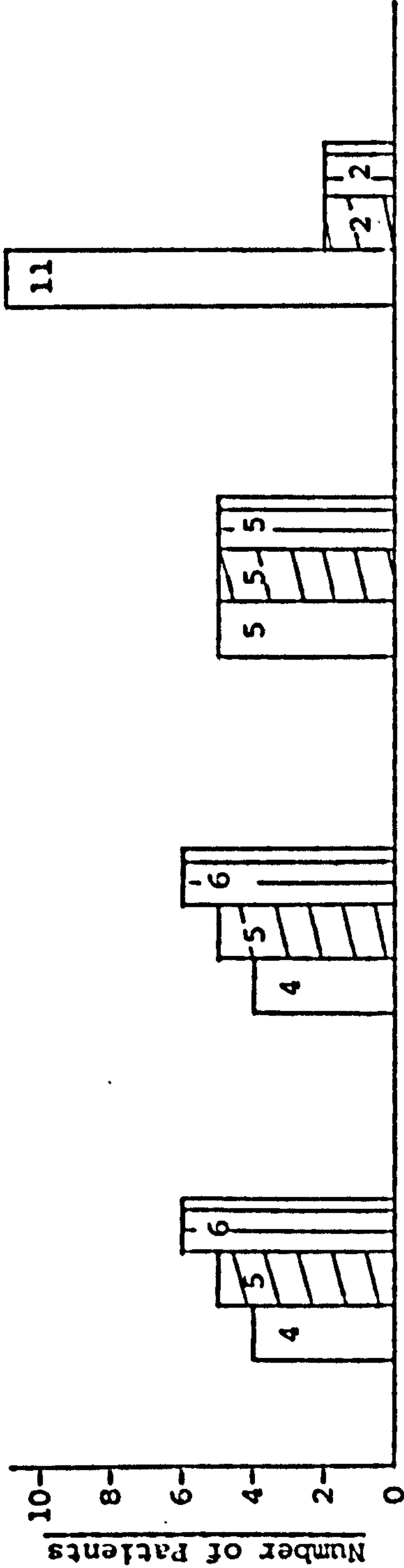


FIGURE 6C

SUBJECTIVE COMPARISON OF DIFFERENT TREATMENT GROUPS AFTER 6 WEEKS AND 6 MONTHS

6.3.2 Comparison of Methods of Physiotherapy

The four groups were comparable with respect to age, weight, parity, grade of incontinence, initial pad changes per 24 hours and incidence of incontinence surgery.

Subjective Assessment

The results of the patients subjective response to treatment are presented in Figure 6C . There was little numerical or statistical difference in outcome between each of the three active treatments (Groups 1, 2 and 3) at either the 6 week or 6 month assessment. Approximately one third of the 15 patients in each group felt they were no better, one third felt that they were improved and one third much improved at the completion of treatment and this improvement was maintained in the majority at the 6 month follow-up. However only 4 of the 15 home treatment patients noted any improvement at both the 6 week and 6 month visit. Although this is numerically less than the Hospital treated patients, it was not statistically different ($p > 0.10$ at 6 weeks; $p > 0.30$ at 6 months).

Objective Assessment

The results are summarised in Table 6C.

Number of Urinations per day: The frequencies of urinations were reduced in all the groups. The reductions in the mean numbers of urinations per 24 hours were

greater in the three Hospital treated groups than in the home treatment group but not significantly so ($F\{3,53\} = 0.649, p = 0.587$).

Pad Changes per Day: All the treatment groups showed a reduction in pad changes and the mean reductions in numbers of pad changes for the four groups were 54, 43, 52 and 11% respectively. The reductions in the Hospital treated patients (Groups 1 - 3) were all statistically significant at the 10% level ($0.05 > p < 0.10$) but the reduction in the home treatment group (4) was not ($p > 0.10$).

Perineometry: The perineometry readings were increased in all the groups and the changes in the mean perineometer readings ranged from 224% in group 3 (PFE + Interferential therapy), to 19% in the home treatment group. The changes in groups 3 and 1 (PFE in Hospital) were statistically significant at the 5% level ($p < 0.05$) while the change in the faradism group was significant at the 10% level ($0.05 < p < 0.10$). The increase in the home treatment group was not statistically significant ($p > 0.10$).

Urethral Pressure Profiles

Maximum Urethral Closure Pressure (MUCP): The mean MUCP was increased in all groups, however only the change in group 3 (PFE + Interferential therapy) was statistically significant (50.7 cms H_2O before treatment

56.0 cms H₂O after treatment) ($p < 0.05$).

Maximum Urethral Closure Pressure measured during pelvic floor contraction (MUCP + PFC): The mean MUCP + PFC was also increased in all the groups, however the increases in this parameter observed in the four groups were not significantly different ($f \{3,40\} = 0.725$, $p = 0.543$).

Urilos Nappy Test

A sensible statistical analysis was impossible as the number of patients in each group from whom urilos data were available was small and the data was extremely variable.

The attendance rates to the Physiotherapy Department were noted to be better in the faradism and interferential therapy groups when compared with those receiving pelvic floor exercises alone.

PARAMETER	Group 1 (PFE in Hospital)	Group 2 (PFE & Faradism)	Group 3 (PFE + Inter-ferential therapy)	Group 4 (PFE at home)
Urinations/24 hours Mean - Before Treatment After Treatment n	8.63 7.60 15	8.72 7.82 15	9.07 8.03 15	8.25 8.21 12
Pad Changes/24 hours Mean - Before Treatment After Treatment n	2.00 0.93 15	2.33 1.33 15	3.30 1.57 15	3.07 2.73 15
Perineometry Reading (mm Hg) Mean - Before Treatment After Treatment n	7.1 15.7 15	5.8 9.0 15	5.1 16.5 15	5.8 6.9 14
Maximum Urethral-Closure Pressure (ccs H ₂ O) Mean - Before Treatment After Treatment n	49.6 51.1 9	56.1 58.0 14	50.7 56.0 12	49.8 53.4 10
Maximum Urethral Closure Pressure + Pelvic Floor Contraction (ccs H ₂ O) Mean - Before Treatment After Treatment n	58.3 62.3 9	62.8 64.4 14	58.1 62.7 12	57.6 62.2 9

TABLE 6C

OBJECTIVE COMPARISON OF DIFFERENT TREATMENT GROUPS

6.3.3 Factors contributing to success or failure of Physiotherapy Treatment

A comparison of the 17 patients considered to be "successes" (i.e. much improved) with the 13 "failures" (i.e. no better) is presented in Table 6D. The most significant factor associated with successful treatment was the initial number of pad changes per 24 hours; this was 1.8 in the successes compared with 3.9 in the failures ($p < 0.005$). The successful patients were also significantly younger (43.8 years compared with 52 years, $p < 0.05$) and they had less evidence of urethral incompetence on radiological screening (mean grade of incontinence* was 1.4 in successes compared with 1.8 in failures, $p < 0.025$). Their initial maximum urethral closure pressures both resting and during pelvic floor contraction were significantly higher than the failures and their Urilos Nappy Test before treatment showed significantly less leakage (0.8 ccs per 2 hours compared with 7.3 ccs per 2 hours, $p < 0.05$). None of the successful patients had had previous incontinence-correcting surgery compared with 6 of the 13 failures (5 had had previous pelvic floor surgery and 1 had had a retropubic procedure). This difference in incidence of previous surgery was also statistically significant ($p < 0.05$). The non significant factors associated with successful treatment included parity, weight, urinations per 24 hours and initial perineometer reading.

*Reference 1.3.8.

Significant Factors	Successes (Mean \pm SD)	Failures	Statistical Significance
Age	43.8 \pm 10.1	52 \pm 11.9	p < 0.05
Initial pad changes per 24 hours	1.8 \pm 1.4	3.9 \pm 2.0	p < 0.005
Radiological grade of Incontinence, ** Grade 1 - Open Proximal Urethra, Grade 2 - Open Proximal Urethra plus leakage	1.4 \pm 0.5	1.8 \pm 0.4	p < 0.025
Initial maximum urethral closure pressure (cms H ₂ O)	59.6 \pm 16.5	46.6 \pm 15.9	p < 0.05
Initial maximum urethral closure pressure plus levator contraction (cms H ₂ O)	70.1 \pm 10.3	53.1 \pm 17.4	p < 0.02
Incidence of previous Incontinence - correct- ing Surgery	0	0.46 \pm 0.52	p < 0.05 *
Urilos Nappy Test (cc/2 hours)	0.8 \pm 1.3	7.3 \pm 9.9	p < 0.05
Non-Significant Factors			
Parity	2.2 \pm 1.3	2.5 \pm 1.1	NS
Weight (Kgs)	63.3 \pm 10.6	67.3 \pm 5.0	NS
Urinations/24 hours	9.2 \pm 2.8	7.9 \pm 3.5	NS
Initial perineometry Reading (mm Hg)	6.1 \pm 5.5	5.1 \pm 3.7	NS

Analysis by two sample Student 't' Test except Incidence of Incontinence Surgery * which was done by the Fisher Exact Test.

** See 1.3.8.

TABLE 6D

COMPARISON OF THE 17 PATIENTS CONSIDERED TO BE "SUCCESSSES"
WITH THE 13 "FAILURES" OF THE 45 PATIENTS RECEIVING HOSPITAL
BASED PHYSIOTHERAPY

6.4 DISCUSSION

The results of the subjective and objective assessments confirm the benefits of intensive hospital-based physiotherapy in patients with genuine stress incontinence. The patients studied were a selected population in that they were referred for assessment to a multidisciplinary urodynamic referral centre and approximately 20% had undergone previous incontinence correcting surgery. However over two thirds of them were improved by hospital-based physiotherapy and this effect was sustained in the majority at six months with 27% of the patients being dry or almost dry at this time and not requiring further treatment. A longer study is required to more exactly assess the duration of this beneficial effect.

Regarding the objective parameters examined before and after treatment, there was a significant reduction in leakage, as recorded by pad changes per 24 hours and the Urilos Nappy Test, and frequency of urinations. The mechanism of this reduction in urinations with physiotherapy is unknown but noteworthy and it may add support to the theory that pelvic floor contraction can inhibit the detrusor motor nucleus (Bradley et al 1974, Brindley et al 1974). More simply, this urination reduction could be explained also by less fear of leakage with treatment, as women often compensate for their incontinence by frequency to keep their bladder empty. Although there was a statistical reduction in the frequency of urinations per 24 hours, from 8.9 to 7.9,

this is probably of only minimal clinical significance.

The significant increases in the maximum urethral closure pressure and perineometer readings with treatment may suggest that both the urethral and peri-urethral striated muscles are affected by physiotherapy. However, further studies would need to be done before this could be substantiated. Caution should also be observed in the interpretation of the 4 cm mean increase in the urethral pressure profile following treatment as the instrumental contribution to result variability has been estimated for consecutive measurements by Abrams et al (1978), to be 4 cms of water.

The addition of interferential therapy or faradism did not appear to confer any significant benefit over pelvic floor exercises alone but the three groups of hospital based patients showed significant improvement when compared with the home treatment group. The attendance of those patients receiving interferential therapy or faradism was better than those receiving pelvic floor exercises alone. This finding was noted also by Scott and Hsueh (1979) in their study using galvanic vaginal muscle stimulation; they attributed this phenomena to better patient motivation with the additional instrument.

This data confirm the findings of Kegel (1948) and Mandelstam (1976) that the perineometer is a useful device for teaching the patient the pelvic muscles to contract.

Also it allows some objective assessment of muscle contractility and encourages patients during treatment. All the exercises and treatment were supervised by two physiotherapists and the success of this treatment probably is as dependent on the enthusiasm of the staff as on patient motivation.

The severity of incontinence was shown to be a significant prognostic indicator as mild-moderate incontinence was improved more consistently by physiotherapy than severe leakage. Jones and Kegel (1952) did not observe this phenomenon nor did they find failure of treatment to be associated with previous incontinence correcting surgery and older age as indicated by this work. In this study, the "successful" factors of younger age and less pelvic floor surgery could be explained by better tone and less fibrosis of the pelvic floor musculature although other factors may also be involved.

CHAPTER 7

STEROID HORMONE RECEPTORS IN THE

FEMALE LOWER URINARY TRACT

7.1 INTRODUCTION

The female lower urinary tract and lower genital tracts have similar embryological origins arising from the primitive urogenital sinus and the lower urinary tract appears to be sensitive to both oestrogen and progesterone (1.5.1; 1.5.2). In the human, specific oestrogen and progesterone receptors have been found in the genital tract but there are no published reports of the presence of these receptors in the female lower urinary tract. A study was carried out to estimate the level of cytosol oestrogen and progesterone receptors in this site.

7.2 MATERIAL AND METHODS

7.2.1 Samples

Twenty-nine full thickness biopsies were obtained from the vault trigone and urethra of 9 female patients aged 13 - 72 years undergoing surgery for various reasons as indicated in Table 7A. The three patients, numbers 7, 8 and 9 who had a cystectomy carried out for bladder carcinoma had received deep x-ray therapy, 2, 4 and 10 years previously respectively. In addition biopsies were taken from the vagina, cervix and myometrium of patient number 9 for comparison. The samples were freed from fat and surrounding connective tissue, were transported in liquid nitrogen and stored in a cryofridge (-70°C) and used for assay within 14 days.

7.2.2 Oestradiol 17B Receptors (E_2R) Cytosol Assay

Assays were performed using tritium labelled oestradiol and separating firmly bound from free oestradiol by precipitation with dextran/charcoal (Taylor 1974). A series of 6 point Scatchard plots were constructed (Scatchard 1949). In the assays specific and non-specific binding of oestradiol were distinguished.

7.2.3 Progesterone Receptor (PgR) Cytosol Assay

The same procedure was used as in the E_2R assay except that a tritiated progestogen (R5020 New England Nuclear) was used in place of oestradiol.

7.2.4 Protein Determination

The protein content of the cytosol was determined by the method of Lowry et al (1951) with bovine serum albumin as standard.

7.2.5 Analysis of Data

A Scatchard plot is shown in Figure 7A . The slope of the line gives the dissociation constant (K_D), a measure of the tightness of the binding between oestradiol and the receptor molecule while the intercept on the abscissa gives the number of binding sites in the sample by calculation.

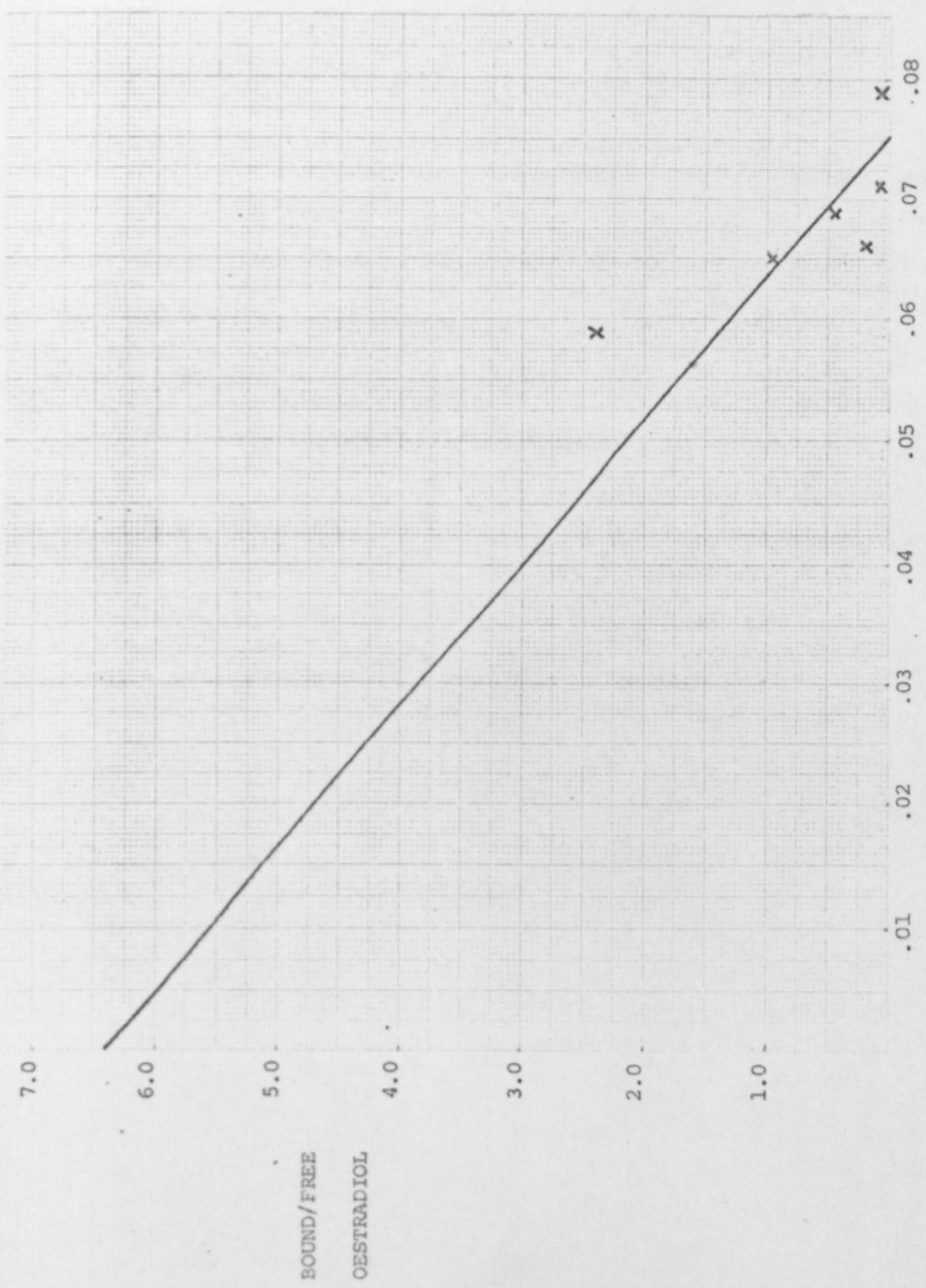


FIGURE 7A

BOUND OESTRADIOL (P mols/ml of incubate)

A SCATCHARD PLOT TO DETERMINE THE BINDING CONSTANT FOR OESTRADIOL RECEPTORS AND THE NUMBER OF BINDING SITES PRESENT (SAMPLE OF MID-URETHRA FROM PATIENT NUMBER 8)

7.3 RESULTS

The results are summarised in Table 7A.

7.3.1 Oestrogen Receptors

Oestrogen receptors were present in all 5 urethral specimens examined and with a consistently higher concentration in the middle and distal thirds in comparison to the proximal urethra. In only one of the 9 vault specimens and 8 trigone specimens were receptors found and those in small quantities.

The level of the E_2R in the vagina, cervix and myometrium of patients 9 was 53.9, 59.1 and 212.0 fm/mg protein respectively. All the dissociation constants fell within the accepted range for E_2R .

7.3.2 Progesterone Receptors

No progesterone receptors were measured in any of the vault, trigone and urethral specimens examined. Progesterone binding was present in the myometrium but in such low concentrations that a satisfactory Scatchard plot could not be produced. No progesterone receptors were measured in the specimens of cervix or vagina.

PATIENT NUMBER AND AGE	REASON FOR SURGERY	SAMPLE	OESTROGEN RECEPTOR		PROGESTERONE RECEPTOR	
			fm/mg of Cytosol protein	KDx10 ⁻¹⁰ M	fm/mg of Cytosol protein	KDx10 ⁻¹⁰ M
8. 63 Years))))))) Cystectomy for bladder carcinoma	Vault	N.D.	N.D.	N.D.	N.D.
		Trigone	N.D.	N.D.	N.D.	N.D.
		P.U.	B	B	N.D.	N.D.
		M.U.	80.6	0.1177	N.D.	N.D.
		D.U.	60.0	0.2054	N.D.	N.D.
9. 72 Years))))))) Cystectomy for bladder carcinoma	Vault	N.D.	N.D.	N.D.	N.D.
		Trigone	N.D.	N.D.	N.D.	N.D.
		P.U.	B	B	N.D.	N.D.
		M.U.	37.0	0.5070	N.D.	N.D.
		D.U.	59.1	0.6452	N.D.	N.D.
		Myometrium	212.9	0.4799	N.D.	N.D.
		Cervix	59.1	0.4286	N.D.	N.D.
		Vagina	53.9	0.8568	N.D.	N.D.

N.D. No receptors measured.
B Specific oestradiol binding was present but a satisfactory Scatchard plot could not be produced.
P.U. Proximal 1/3 urethra.
M.U. Mid 1/3 urethra.
D.U. Distal 1/3 urethra.

7.4 DISCUSSION

Although this is a preliminary report with relatively small numbers, the results clearly show for the first time that there are oestrogen receptors in the human female lower urinary tract predominantly in the middle and distal thirds of the urethra. The presence of these receptors confirms that the urethra is an oestrogen "target" organ and provides objective evidence of the urethral sensitivity to oestrogens as outlined earlier (1.5.1).

The higher concentration of oestrogen receptors in the distal and middle thirds of the urethra in comparison to the proximal urethra and bladder may possibly be a reflection of the different anatomy and embryology of these tissues since the distal urethra (and vagina) arise from the definitive urogenital sinus and the proximal urethra and bladder originate from the vesicourethral canal (1.5.1). Although the numbers were small, the distal and middle urethral cytosol receptor concentration was similar to that in the vagina (Wiegerinck et al 1980). The results also confirm the animal studies of Lindskog et al (1980) who found oestrogen receptors in the rat urethra (in a similar concentration to the vagina) and not in the bladder.

The absence of measurable progesterone receptors in all the lower urinary tract specimens is surprising in view of the possible sensitivity of the urethra to progesterone as outlined previously (1.2.2). An explanation of this

could be either the assay, the receptor itself or the patients used. The assay for progesterone receptor has only recently been developed in our Unit and though high levels of receptor have been demonstrated, difficulty has been experienced in the lower level assays. Receptor levels were measured in the genital tract as a comparison and though the oestrogen levels were within the expected range for these tissues the one progesterone estimation in the myometrium was far lower. In addition, the progesterone receptor is more unstable with regard to temperature and the presence of glycerol, and 3 of the patients had received radiotherapy previously which could have destroyed the receptor protein (Young et al 1976).

However, from the results of this study, if progesterone acts on the urethra and bladder, it does so by mechanisms other than through a physiological steroid receptor interaction. The same may apply to oestrogen with regard to effect on the bladder.

The clinical implications of the identification of oestrogen receptors in the human female urethra, is that it now provides an objective basis for the use of oestrogens in cases of atrophic urethritis and the "urethral syndrome" (Smith 1976). The use of oestrogens in urethral dysfunction incontinence (Genuine Stress Incontinence) is discussed in the next Chapter.

CHAPTER 8

TREATMENT OF GENUINE STRESS INCONTINENCE

IN POSTMENOPAUSAL WOMEN WITH SYSTEMIC OESTROGENS

8.1 INTRODUCTION

Oestrogen deficiency leads to atrophy of the urethral mucosa (Smith 1972) and is believed to be a contributory factor in genuine stress incontinence (Hald 1975, Stanton 1977). However in the treatment of genuine stress incontinence the evidence is conflicting that oestrogens are effective (1.5.5). Since oestrogen receptors were identified in the female urethra in the previous study, to ascertain further the role of oestrogens in incontinence, a prospective trial was conducted to evaluate the effect of piperazine oestrone sulphate (harmogen) on post-menopausal women presenting with genuine stress incontinence.

8.2 PATIENTS AND METHODS

8.2.1 Patients and Study Design

36 patients aged 47 to 72 years (mean age of 57.2) were studied. 30 had experienced a natural menopause between 1 to 24 (mean 10.1) years previously. 6 patients had had a previous hysterectomy. The serum gonadotrophin concentrations in all the patients were in the post-menopausal range (Jacobs and Murray 1976).

Each had had an independent flow rate (1.2.4) and synchronous video pressure flow cystourethrography carried out (3.2) and had been shown to have stable detrusor function with no outlet obstruction and been diagnosed to have genuine stress incontinence. In 10 patients the Fluid Bridge Test (3.4) was performed also.

No patient had received oestrogen or progesterone treatment in the preceding 3 months and there were no medical contraindications to oestrogen therapy. Prior to the study a full clinical examination was carried out including screening for breast and genital cancer and weight and blood pressure were recorded. All the patients had negative urine cultures before, during and after the treatment.

The trial design was a double blind comparative study. Each patient was randomly allocated to 3 months treatment with either piperazine.oestrone sulphate

(Harmogen) (2 x 1.5 mgs tablet nocte) in 3 weekly courses with one treatment-free week between each course or a matching placebo (2 tablets nocte) taken in an identical manner. The patients were told that the tablets were of different strength and every patients G.P. was informed that a placebo trial was being conducted.

8.2.2 Subjective Assessment

Subjective assessment was carried out at six weeks and at the last week of treatment (week 11) when the patients were asked if they were much improved, improved or no better. The patients in both groups who responded to therapy (i.e. the first two categories) were further assessed at 6 and 12 weeks after the tablets were discontinued.

8.2.3 Objective Assessment

1. Bladder Charts

7 day bladder charts (1.3.2) were filled in for the week before start of treatment (Week -1), for the first, 6th and last week of treatment (Week 11).

Those patients who responded to therapy also completed a bladder chart, 6 and 12 weeks after the tablets were discontinued.

2. Urilos Nappy Test

This was carried out as described previously (3.5) in

22 patients for 2 hours of normal activity, before the start and on completion of the 3 months course of treatment.

3. Urethral Pressure Profile

The Urethral Pressure Profile using the method of Brown and Wickham (3.3) was also estimated before the start and on completion of the three months course of treatment.

4. Vaginal Cytology

Lateral vaginal smears were taken before the start, at the 6th and during the final week of therapy. A saline moistened cotton tipped swab was used to obtain cells from the upper outer third of the vaginal wall. The smears were fixed in 95% alcohol and stained by the method of Papanicolau and Traut (1943). All specimens were examined by the same cytologist and 50 cells were evaluated in each smear using Frosts random counting method (1967). The proportion of oestrogenised superficial cells to intermediate and parabasal cells were determined and expressed as a percentage of the total cell count to give the karyopyknotic index (KI). The differential count was also converted to a "maturation value" (Meisels, 1967) by multiplying the percentages of the various cell types by varying factors (1.0 for superficial cells, 0.5 for intermediate cells and 0 for parabasal cells) and summing the products.

5. Hormone Estimations

Blood Samples - Blood samples were collected from 25 patients in the morning before therapy and at the end of the sixth and eleventh week of treatment (the 20th or the 21st day of the last cycle). The blood was put in a dry glass tube allowed to clot and the resultant serum stored at -25°C to wait analysis.

Hormone Determinations - Oestrone and oestradiol were measured in all samples using steroid fractionation and radioimmunoassay as described by Large and Anderson (1979). This involved a preliminary chromatographic separation on celite columns to reduce cross reactivity between oestrone and oestradiol with the antiserum.

Serum follicle stimulating hormone (FSH) and serum luteinizing hormone (LH) were determined by radioimmunoassay techniques based upon the Recommended Procedures of the Supraregional Assay Service for Gonadotrophins, which were kindly made available by Professor S.L. Jeffcoate of the Chelsea Hospital for Women. The procedures were modified for the study to give working ranges of 2 - 200 U/L serum. The standards used were from the National Institute for Biological Standards and Control: for LH 68/40 and for FSH 69/104. The within-assay coefficients of variation were 7.4% for LH and 5.1% for FSH and the between-assay CV were 10.2% for LH and 9.5% for FSH ($n = 1.5$).

8.2.4 Statistical Analysis

36 patients were admitted to the study: 18 were treated with oestrogen and 18 with placebo. However 2 patients in the oestrogen group failed to complete the study (see below). Therefore the statistical analysis was restricted to the 16 Harmogen treated and the 18 placebo treated patients.

The demographic data for the 2 patient groups were compared using the two-sample Student t-test, Mann Whitney U-test and Fishers exact test (see Appendix).

The results of treatment were compared using a standard analysis of variance (see Appendix).

8.3 RESULTS

The two treatment groups were comparable with respect to all the demographic variables measure (Table 8A). However the oestrogen patients were on average 4 cm taller than the placebo patients. This difference, although numerically small, was extremely close to the statistical significance at the 5% level.

8.3.1 Subjective Assessment

7 out of the 16 oestrogen treated patients said they were much improved, 5 were improved and 4 were no better on completion of treatment. However, 5 of the 18 placebo treated patients were much improved, 5 were improved and 8 no better (Table 8B). The differences between the 2 treatment groups were not statistically significant ($p < 0.40$).

8.3.2 Side Effects

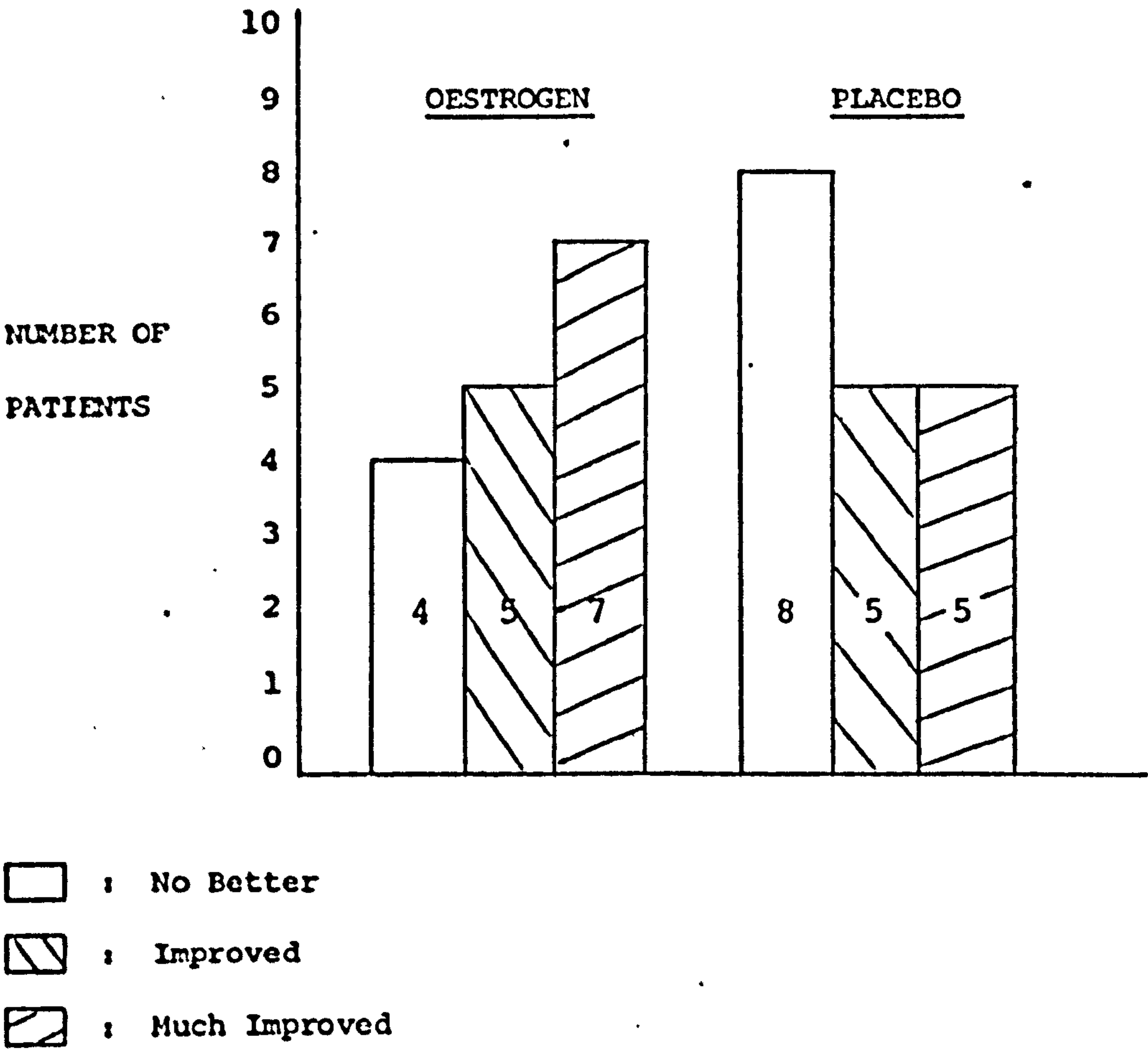
2 patients in the oestrogen treated group failed to complete the study. One complained of palpitations and trembling 5 days after starting treatment and the other suffered a posterior subendocardial infarct during an emotional argument 5 weeks after the start of the study. The other side effects are listed in Table 8C and were not significantly increased on oestrogen therapy.

Factor		Treatment Group: Oestrogen Placebo		Statistics
Age (years)	Mean	57	58	t(32) = 0.438 (p = 0.668)
	S.D.	7	6	
	Range	47 - 72	50 - 70	
Height (cms)	Mean	161	157	t(30) = 1.991 (p = 0.053)
	S.D.	6	5	
	Range	147 - 169	148 - 167	
Weight (kgs)	Mean	66.9	63.4	t(32) = 1.297 (p = 0.201)
	S.D.	8.1	7.6	
	Range	55.5 - 79.4	52.0 - 77.6	
L.M.P. (years)	Median	8	13	Mann-Whitney U = 82 (p = 0.316)
	Range	1 - 24	2 - 21	
Parity	0	2	1	Mann-Whitney U = 103 (p = 0.158)
	1	2	4	
	2	1	6	
	3	6	5	
	4	1	2	
	5 +	4	0	
Duration of Symptoms (years)	Median	4	5	Mann-Whitney U = 111 (p = 0.521)
	Range	1 - 40	1 - 24	
Grade of Incontinence *	1	5	9	Fisher's Exact Test (p = 0.315)
	2	11	9	
Previous Pelvic Surgery (Number of Operations)	0	11	9	Fisher's Exact Test (p = 0.217)
	1	4	9	
	2	1	0	

*See 1.3.8.

TABLE 8A

ANALYSIS OF DEMOGRAPHIC DATA IN BOTH
TREATMENT GROUPS



SUBJECTIVE COMPARISON OF PLACEBO AND OESTROGEN
THERAPY AT COMPLETION OF TREATMENT (WEEK 11)

TABLE 8B

SIDE EFFECT	OESTROGEN	PLACEBO
Subendocardial Infarct	1	0
Chest Pain (Normal E.C.G.)	1	1
Leg Pain	0	1
Palpitations	1	0
Breast Discomfort	1	2
Vaginal Bleeding	1	1
Interval Headache	0	1
Nausea	1	1

TABLE 8C**SIDE EFFECTS DURING PLACEBO AND****OESTROGEN ADMINISTRATION****(Results are numbers of patients)**

8.3.3 Objective Assessment

Numbers of urinations and pad changes per day

The frequencies of urinations were reduced in both treatment groups, although the reduction in the oestrogen treated patients (1.6 urinations per 24 hours) was numerically greater than the placebo treated patients (0.3 urinations per 24 hours), this was not statistically significant (Table 8D).

The numbers of pad changes per 24 hours were also reduced in both treatment groups. The reduction in the oestrogen group (1.6 pad changes per 24 hours) was significantly greater than the placebo group (0.6 pad changes per 24 hours) at week 6 ($F(3,94) = 2.614$, $P = 0.056$). However at the end of the 3 months treatment period the improvement in the oestrogen group (1.5 pads per 24 hours) was not significantly different from the placebo (0.9 pads per 24 hours).

12 of the 16 "oestrogen" patients (i.e. 75%) and 10 of the 18 placebo treated patients (56%) were judged to have "responded" to therapy based on their subjective assessment plus bladder charts. These 22 patients attended for follow up at 6 and 12 weeks after the tablets were discontinued. (Table 8Dii). An analysis of the 22 responders showed no difference between the two treatment groups for either parameter ($f(5,94) = 0.430$, $P = 0.827$ for urinations; $f(5,95) = 1.407$; $P = 0.229$ for pad changes}. It did show however that the improvements obtained with

i) All 34 Patients

<u>Week</u>	<u>Factor</u>	Number of Urinations per Day:		Number of Pad Changes per Day:	
		<u>Oestrogen</u>	<u>Placebo</u>	<u>Oestrogen</u>	<u>Placebo</u>
- 1	Mean 95% c.l.	10.0 (8.6-11.5)	10.7 (9.3-12.2)	2.5 (1.5-3.8)	2.6 (1.6-3.9)
1 st	Mean 95% c.l.	9.1 (7.7-10.5)	10.4 (9.1-11.9)	1.3 (0.6-2.2)	2.2 (1.3-3.3)
6 th	Mean 95% c.l.	8.6 (9.3-10.1)	10.0 (8.7-11.4)	0.9 (0.3-1.7)	2.0 (1.1-3.1)**
11th	Mean 95% c.l.	8.4 (7.1-9.8)	10.4 (9.0-11.9)	1.0 (0.4-1.9)	1.7 (1.0-2.8)

ii) "Responders" Only

<u>Week</u>	<u>Factor</u>	Number of Urinations per Day:		Number of Pad Changes per Day:	
		<u>Oestrogen</u>	<u>Placebo</u>	<u>Oestrogen</u>	<u>Placebo</u>
- 1	Mean 95% c.l.	9.9 (8.5-11.4)	10.5 (8.9-12.2)	2.5 (1.1-4.5)	2.6 (1.3-4.3)
1 st	Mean 95% c.l.	8.7 (7.4-10.1)	10.3 (8.7-12.0)	1.0 (0.2-2.3)	1.9 (0.8-3.4)
6 th	Mean 95% c.l.	8.0 (6.8-9.4)	9.3 (7.8-10.9)	0.6 (0.1-1.8)	1.7 (0.7-3.2)
11th	Mean 95% c.l.	7.9 (6.7-9.2)	9.1 (7.7-10.8)	0.6 (0.1-1.7)	1.0 (0.3-2.2)
17th	Mean 95% c.l.	7.8 (6.6-9.2)	8.8 (7.3-10.4)	0.4 (0-1.4)	1.3 (0.4-2.6)
23rd	Mean 95% c.l.	8.1 (6.8-9.5)	9.2 (7.7-10.8)	0.6 (0.1-1.7)	1.2 (0.4-2.5)

c.l. = Confidence limits.

** $p < 0.10$

week - 1 = 7 days preceeding treatment.

TABLE 8D

EFFECT OF TREATMENT WITH PLACEBO OR OESTROGENS ON
NUMBERS OF URINATIONS AND PAD CHANGES PER DAY

both oestrogen and placebo were maintained for at least 3 months after the termination of therapy.

Urethral Profiles

The results of the changes in the maximum urethral closure pressure before the after treatment are shown in Table 8E. The maximum urethral closure pressure fell slightly in both treatment groups but the difference in the falls was not statistically significant { $f(1,29) = 0.011$, $P = 0.915$ }. The effect of oestrogen on M.U.C.P. was not significantly different from that of placebo.

The functional and anatomical urethral lengths were also virtually unchanged following treatment in both groups.

Urilos Nappy Test

The results of the urilos nappy test before and after treatment in the 8 oestrogen and 14 placebo treated patients are shown in Table 8F. The changes were not significantly different for the two treatment groups.

Vaginal Cytology

The effect of oestrogen and placebo treatment on vaginal cytology is shown in Table 8G. Both the KPI and maturation value were significantly increased by oestrogens but unaffected by placebo.

Week	Factor.	Oestrogen	Placebo
0	Mean 95% c.l.	57 (51-62)	53 (49-58)
11	Mean 95% c.l.	53 (48-58)	50 (46-55)

c.l. = Confidence limits.

TABLE 8E

CHANGES IN THE MAXIMUM URETHRAL CLOSURE PRESSURE
(Cms H₂O) BEFORE AND AFTER TREATMENT WITH PLACEBO OR
OESTROGENS

Week	Factor	Oestrogen (mls/2 hrs)	Placebo (mls/2 hrs)
0	Mean 95% c.l.	5 (0-13)	5 (0-12)
11	Mean 95% c.l.	6 (0-14)	3 (-0-10)

c.l. = Confidence limits.

TABLE 8F

URILOS NAPPY TEST

<u>Week</u>	<u>Factor</u>	<u>KPI</u>		<u>Maturation Value</u>	
		<u>Oestrogen</u>	<u>Placebo</u>	<u>Oestrogen</u>	<u>Placebo</u>
0	Mean 95% c.l.	2 (1-4)	2 (1-4)	33.8 (22.9-41.7)	37.8 (30.4-45.1)
6	Mean 95% c.l.	25 (14-43)	3 *** (2-6)	70.3 (62.4-78.2)	41.8 *** (34.4-49.1)
11	Mean 95% c.l.	20 (12-35)	3 *** (1-6)	69.7 (61.8-77.5)	39.9 *** (32.5-47.2)

c.l. = Confidence limits.

*** = $p < 0.01$.

TABLE 8G

THE EFFECT OF OESTROGEN AND PLACEBO
TREATMENT ON VAGINAL CYTOLOGY

Hormone Assays

The effects of oestrogen and placebo on serum gonadotrophins and plasma oestrogens are shown in Table 8H and 8I. The effect of oestrogen on LH levels was not significantly different from that of placebo. However the FSH levels were significantly reduced by oestrogen but unaffected by placebo. Both the serum oestrone and oestradiol levels were significantly increased by oestrogen but unaffected by placebo.

<u>Week</u>	<u>Factor</u>	<u>FSH (I.U./l)</u>		<u>LH (I.U./l)</u>	
		<u>Oestrogen</u>	<u>Placebo</u>	<u>Oestrogen</u>	<u>Placebo</u>
0	Mean 95% c.l.	87 (73-101)	84 (70-97)	43 (37-48)	40 (35-46)
6	Mean 95% c.l.	47 (33-61)	82 *** (69-95)	33 (27-39)	39 (34-44)
11	Mean 95% c.l.	54 (40-68)	80 *** (67-93)	38 (33-44)	38 (33-43)

c.l. = Confidence limits.

*** = $p < 0.01$.

TABLE 8H

THE EFFECT OF OESTROGEN AND PLACEBO TREATMENT
ON SERUM GONADOTROPHINS

<u>Week</u>	<u>Factor</u>	<u>Oestradiol (p mol/l)</u>		<u>Oestrone (p mol/l)</u>	
		<u>Oestrogen</u>	<u>Placebo</u>	<u>Oestrogen</u>	<u>Placebo</u>
0	Mean 95% c.l.	82 (51-132)	83 (53-131)	137 (74-253)	241 (135-430)
6	Mean 95% c.l.	314 (195-503)	118 *** (75-186)	1281 (697-2354)	220 *** (123-393)
11	Mean 95% c.l.	409 (255-655)	90 *** (57-141)	1341 (729-2463)	203 *** (113-363)

c.l. = Confidence limits.

*** = $p < 0.010$.

TABLE 8I

THE EFFECT OF OESTROGEN AND PLACEBO TREATMENT
ON PLASMA OESTROGENS

8.4 DISCUSSION

Regarding the benefits of oestrogen therapy in genuine stress incontinence, in this 3 month study, oestrogens were shown to cause a significant reduction in pad changes in comparison to placebo after 6 weeks of therapy. However, on completion of the course, on account of the definite placebo response, there was no significant difference between the 2 groups. The pad change improvements were also maintained equally by both the oestrogen and placebo treated patients for 3 months after cessation of therapy.

With any form of medication the benefits of treatment have to be weighed against the risks and adverse side effects. Although the incidence of side effects was essentially similar in both oestrogen and placebo treated patients, oestrogen therapy is not without risks. Endometrial cancer (Smith et al 1976, Ziel and Finkle 1976), gallbladder disease (Boston Collaborative Drug Surveillance Programme 1974) and possibly thromboembolism (Gow and McGillivray 1971, Coope et al 1975) and breast cancer (Hoover et al 1976) may be enhanced by oestrogen use. The benefits of oestrogens in genuine stress incontinence have to be weighed against these risks and although these will vary from one woman to another, the results of this study indicate that oestrogen use in this condition would appear to be limited. Also in this trial, unopposed oestrogens were given cyclically and this is associated (in approximately 30% of

patients) with both cystic glandular and atypical hyperplasia of the endometrium, (Whitehead et al 1978) and the addition of a progestogen for 5 - 7 days each month has been recommended now to protect against the oestrogen-induced hyperstimulation of the endometrium (Whitehead et al 1978). Although no progestogen receptors were identified in the urethra in the previous study, progestogens have been shown to increase incontinence (Caine and Raz 1973) and therefore they also may offset any benefit of oestrogen therapy when given in combination for genuine stress incontinence.

The findings of this study are similar to the double blind objective study of Walter et al (1976) who unlike Caine and Raz (1973) did not find any significant effect of oestrogen therapy on either incontinence or the urethral pressure profile. The results of Caine and Raz, along with the other non-controlled studies of Salmon et al (1941) and Musiani (1972) which indicated improvement with oestrogens, could be explained by placebo effect.

The significant changes in vaginal cytology and hormone assays with oestrogen treatment confirmed that the patients received the medication. The pre and post treatment plasma levels of oestrone and oestradiol were similar to those recorded by Hutton (1979) after oral administration of 3 mgs of Piperazine oestrone sulphate. They confirmed that the term hormone "replacement" therapy is inappropriate since the levels of oestrone were consistently higher than both premenopausal values and also

oestradiol, the dominant oestrogen when ovarian function is active.

The trial design was a double blind comparative study and the other alternative to this would have been a double blind cross over study. In view of the duration of the placebo response (at least 3 months after cessation of therapy), it is unlikely that a cross over regime would have given any more additional information.

CHAPTER 9

CONCLUSIONS

CONCLUSIONS

This thesis has examined aspects of aetiology, investigation and conservative treatment of female genuine stress incontinence by a series of studies and from them several conclusions can be drawn:

Aetiology of Genuine Stress Incontinence

1. It is unlikely that altered morphology of the posterior pubo-urethral ligaments is an aetiological factor in genuine stress incontinence.
2. The term posterior pubo-urethral "ligament" may be a misnomer as these structures contain contractile elements under possible neural control.

Investigation of Genuine Stress Incontinence

1. The importance of studying postural influences on cystometry in detecting detrusor instability is confirmed.
2. This posture effect is also related to age, supine tests detecting a higher percentage of detrusor instability as age increases.
3. The Fluid Bridge Test produces better correlation with cystourethrography when performed in the erect rather than supine position, however, overall it is less reliable than cystourethrography in the diagnosis of

genuine stress incontinence.

4. While the Uriilos System is an excellent concept in principle and appears to confirm even minimal incontinence, because of the major problems of under- or over-recordings between nappies and poor reproducibility between packs of nappies it is not as yet a sufficiently reliable method of quantifying incontinence.

Conservative Treatment of Genuine Stress Incontinence

The Value of Physiotherapy

1. Physiotherapy is a useful treatment for selected incontinent patients, the effect lasting in the majority when assessed at six months and it may obviate the need for surgery.
2. The addition of interferential therapy and faradism does not appear to confer any significant benefit over pelvic floor exercises alone, however, hospital-based therapy is more effective than home treatment.
3. The factors influencing the outcome of physiotherapy treatment include the patients age, the presence of previous pelvic floor surgery and the degree of incontinence as assessed radiologically, by pad changes and by the Uriilos Nappy Test.

Role of Oestrogens

1. Oestrogen receptors are present in the human female lower urinary tract predominantly in the middle and distal thirds of the urethra thus providing objective evidence that the urethra is an oestrogen "target" organ.
2. The results of the double blind objective study of the treatment of genuine stress incontinence with systemic oestrogens suggest that the known risks of this therapy are greater than its predominantly placebo benefit.

APPENDIX

STATISTICAL ANALYSIS

The Statistical tests used in the physiotherapy and oestrogen studies are outlined briefly below.

(i) Student t-Test

A sample is obtained from each of 2 normally distributed populations. The means and standard deviations of the 2 populations are unknown so are estimated from the samples. The Student t-Test is used to test the Null Hypothesis that the means of the 2 populations are equal.

A) Independent samples

The samples are obtained from 2 different groups of patients. The t-statistic has the form:

$$t = \frac{\text{Difference between the sample means}}{\text{Standard deviation of the difference between the sample means}}$$

and has $(n_1 + n_2 - 2)$ degrees of freedom, where n_1 is the number of patients in the first sample and n_2 is the number of patients in the second sample.

B) Paired data

The 2 samples are obtained from a single group of patients i.e. each patient contributes an observation to each sample. The difference between the pair of observations is calculated for each patients. The t-statistic has the form:

$$t = \frac{\text{Mean of the differences}}{\text{Standard deviation of the differences}}$$

and has $(n - 1)$ degrees of freedom, where n is the number of patients sampled.

In both cases, the t-statistic is compared against Tables of

the t-distribution with the appropriate degrees of freedom. If the t-statistic is smaller than the critical value (at some pre-determined level of significance, e.g. 5%) in the Tables then the Null Hypothesis is accepted. Otherwise the Null Hypothesis is rejected.

(ii) Mann-Whitney U-Test

This test corresponds to the independent samples t-test and applies in situations when the 2 populations being sampled are not normally distributed. The Null Hypothesis tested is simply that the 2 populations have the same (undefined) distributions.

The observations in the 2 samples are combined and given rank scores, i.e.:

The smallest of all the observations is given rank score 1, the next smallest of all the observations is given rank score 2, and so on.

Then, the rank score for the observations in the smaller of the 2 samples are added together to give a total score R. If this sample contains n_1 observations and the larger sample contains n_2 observations, the test-statistic is given by:

$$U = n_1 n_2 + \frac{1}{2} n_1 (n_1 + 1) - R$$

The calculated value of U is compared against Tables of critical values of U (as per the t-test above).

(iii) Fisher Exact Test

A sample is drawn from each of 2 independent populations. The numbers in each sample with a given attribute (e.g. male, P.F.R. score, etc), is counted. Thus:

A sample of size n_1 is drawn from population 1, of whom a proportion p_1 have the attribute;

A sample of size n_2 is drawn from population 2, of whom a proportion p_2 have the attribute;

The Fisher exact test tests the Null Hypothesis that the true proportion is the same for both populations. Probability theory methods are used to calculate the probability of obtaining the observed difference $p_1 - p_2$ (or a larger difference) assuming the Null Hypothesis is true.

If this probability is greater than 0.05 (i.e. 5%) then the Null Hypothesis is accepted. Otherwise the Null Hypothesis is rejected.

Where the number of attributes of interest was greater than 2 (e.g. subjective assessments analysis), the contingency table approximation to this test was used.

(iv) Analysis of Variance

The clinical parameters were subjected to a standard analysis of variance (Winer 1971). A number of hypotheses were tested, the most important of which was the Null Hypothesis:

Ho: the changes in the parameters over time were the same for all the patient groups. If the Null Hypothesis was accepted, no further analysis was required. If, on the other hand, Ho was rejected, multiple comparison methods were used to identify which changes were significant from each other.

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