RADIOFREQUENCY INDUCED THERMAL ENDOMETRIAL ABLATION

-Invention and Primary Assessment

Thesis For The Degree Of

Doctor Of Medicine Of The University Of Leicester

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1991

UMI Number: U041894

UMI

Dissertation Publishing

ProQuest

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'THE purposes of menstruation seem to be especially secured by this function: 1st, the relief of the general system by the discharge of the superabundant blood which during pregnancy is appropriated to the formation and growth of the foetus; 2nd, a vicarious satisfaction of the sexual instinct, thus shielding female chastity...'

.......................oOo........................

'THE purposes of menstruation seem to be especially secured by this function: - 1st, the relief of the general system, by the discharge of the superabundant blood which during pregnancy is appropriated to the formation and growth of the foetus; 2nd, a vicarious satisfaction of the sexual instinct, thus shielding female chastity...'

.....................oOo....................

'HINTS For Preventing frequent, copious or irregular menstruation: the use of hot baths, especially with the addition of mustard, should be avoided; also indulgence in the use of hot, spiced and stimulating food and drinks; living in overheated or badly-ventilated rooms, excessive dancing, excitement from novel-reading, too much sitting and late hours...'

Doctor E H Ruddock MD, 1912

Preface

The invention and development of Radiofrequency Endometrial Ablation (RaFEA) has been, by turns, exciting, frustrating and anxiety-provoking. Although one of the major motives for developing an alternative means of effective endometrial ablation to the hysteroscopically directed modalities was to improve safety, it seems that in using RaFEA, one set of potential dangers may have been exchanged for another set. Whilst the potentially fatal risks of uterine penetration and fluid toxicity are not encountered with RaFEA, the charging of the patient with an electric field for the duration of therapy brings its own risks, requiring very special precautions of their own (see section 2 - safety). At the time of writing, the future role of the technique is still being decided. It may be that the technique requires such specialist monitoring that it is unsuitable for general use, and may be restricted to one or two specialist centres for the treatment of certain patients who cannot be treated easily any other way. What is certain is that safety is of paramount importance, and the adequate training of those concerned and a basic knowledge of RF physics

are both essential to safe practice.

Practiced safely, the technique is highly successful,
and has proved of considerable benefit to hundreds of
patients. However, there have been a number of serious
complications in other centres, each of which has been
analysed in very great detail. These are considered in
section 2 - safety.

Declaration

The concept of using thermal energy which does not rely on simple conduction is my own, and the radiofrequency thermal probe was designed by myself, although Terry Roberts ARCS specified electrical requirements.

All work in this thesis is original, except where clearly stated and indicated by parentheses. No part of this work has been submitted in consideration for a degree or award of any other university.

All experimental work was designed and instigated by myself, with the exception of:

1.   The individual components of the RF thermal probe were made in the medical engineering workshops of the Royal Postgraduate Medical School by Mr. Ray Reid MIMechE.

2.   The components of the original RF generating apparatus were supplied and operated by Terry Roberts ARCS and Mike Prior MSc of the Hyperthermia Unit, Hammersmith Hospital.

3. Haematological studies were supervised by the Department of Haematology at Watford General Hospital.

4. The administration of radioisotopes was supervised by Dr. Terry Smith PhD at the Clinical Research Centre, Northwick Park Hospital.

5. Histochemical studies were performed with the help of Rocket Of London Ltd., and Christine Ince FIBiol, senior MLSO at Watford General Histopathology Department.

All other experimentation in both theoretical and practical aspects was carried out by myself.

Jeffrey Howard Phipps

Charing Cross Hospital, Summer 1991

Acknowledgements

I am indebted to:

Victor Lewis

Terry Roberts

Mike Prior

Murdoch Elder

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Abbreviations

ATU	Antenna Tuning Unit
BS	British Standard
D&C	Diagnostic Curettage
EDTA	Ethylene Diamine Tetra Acetic Acid
59Fe	Radioactive Iron
GHz	Gigahertz
G6P	Glucose-6-Phosphatase
Hz	Hertz
kBq	Kilobequel
kVA	Kilovolt Amp
kW	Kilowatt
MeV	Mega electronvolt
MHz	Megahertz
mW	Milliwatt
Nd-YAG	Neodymium-Yttrium-Aluminium-Garnet
nm	Nanometre
RF	Radiofrequency
SWR	Standing Wave Ratio
μCi	Microcurie
W	Watt

SECTION 1 - INTRODUCTION & BACKGROUND

1.1 - Human Endometrium

1.1.1. Histology

The endometrium is a dynamic, hormone-dependent tissue in which cyclical changes are induced during the menstrual cycle in response to ovarian steroid secretion: oestrogen causes growth and proliferation; progesterone induces differentiation and secretion. The superficial layers slough during menstruation leaving a basal layer of endometrium from which regeneration of both stromal and glandular elements occur. A proliferative endometrium forms during the first half of the menstrual cycle as a result of this glandular and stromal proliferation. Differentiation begins around day 14 of a 28 day cycle in response to the production of progesterone by the corpus luteum. This process of differentiation has two phases: during the first phase the changes are those of active glandular secretion. The second phase involves decidualisation of the stroma. This occurs around day 25 and is initially seen as a perivascular cuffing. During pregnancy this process of stromal decidualisa-

tion proceeds rapidly. The aim of endometrial ablation
is to permanently damage the biological apparatus
responsible for this cycle of degeneration and
regeneration of tissue in order to reduce or eliminate
consequent vaginal bleeding in patients who find the
volume of their loss unacceptable.

1.1.2. Embryological Development

The whole of the uterus, endometrium, myometrium and
serosa are mesodermal in origin (Wynn, 1977). The
uterus develops from a pair of mullerian ducts,
originally described by Johannes Muller in 1825. The
mullerian ducts arise as grooves in the mesothelial
lining of the peritoneal cavity, just lateral to the
mesonephric ducts and the primitive gonads during the
sixth week of fetal life (Faulconer, 1951). The
grooves close and grow caudally in a retroperitoneal
position, turning medially to meet in the midline. By
the ninth week the two mullerian ducts have reached the
urogenital sinus. The gubernaculum crosses the
mullerian ducts and that portion lateral to the
crossing gives rise to the fallopian tubes while the
medial portions fuse to form the uterus. Fusion occurs

as soon as the mullerian ducts meet and the fused ducts and urogenital sinus give rise to the uterovaginal canal (Matejka, 1959). Koff (1933) described the development of the endometrium during fetal life. By 10 weeks the uterus is lined by simple columnar epithelium with basal nuclei and by 17-22 weeks glands begin to develop as outpouchings of the epithelium (Koff, 1933, Pryse-Davies 1974).

Usually by 20 weeks gland development is clearly defined and a loose endometrial stroma is found; the glands begin to branch out about the 26th week and branching is uniformly present by 35 weeks (Pryse-Davies and Dewhurst, 1971). Sub- and supra-vacuolation have been observed but disappear within 80 hours of birth. Hence the fetal endometrium is hormone dependent and menstruation sometimes occurs following oestrogen withdrawal after delivery. Song (1964) described the appearance of the endometrium at birth as either having a proliferative, secretory or even decidualised appearance.

1.1.3. Development From Birth To Puberty

During childhood the endometrium remains inactive and the cells of the epithelium are low columnar or cuboidal. The glands are small with absence of mitosis and exhibit no cyclical hormone response. The endometrium is however responsive to exogenous hormone stimulation. Around the time of puberty, follicle stimulating hormone (FSH) and luteinising hormone (LH) levels gradually rise to reach adult levels (Johnson and Everitt, 1980). There is also an increase in LH secretion at night from early to mid puberty. In late puberty the daytime levels of the LH surges increase until the adult pattern of higher basal levels without diurnal variation is achieved. Functional maturity of the hypothalamus in its production of luteinising hormone releasing hormone (LHRH) is believed to be the trigger to the increased gonadotrophic production by the pituitary which in turn stimulates ovarian steroidogenesis which induces the cyclical changes in the endometrium. Grumbach et al (1974) found that ovulatory menstrual cycles could be established in immature rhesus monkeys using an external pump delivering pulses of LHRH and that switching off the

pump resulted in a return to immature, prepubertal endometrium. This supports the belief that the trigger to puberty is primarily the result of functional maturity being attained within the central nervous system (CNS). There is, however, evidence that both the pituitary and the hypothalamus are highly sensitive to suppression by ovarian steroids during childhood. Ferin et al (1979) found that microinjections of oestradiol into the hypothalamus of ovariectomised monkeys limited pulsatile LH secretion and

using a similar technique, also showed decreasing LHRH secretion by the hypothalamus. Whether a negative oestrogen feedback mechanism or an inherent CNS suppression is responsible for restraining the hypothalamus before puberty is unknown.

Whichever the mechanism, the functionally mature hypothalamus causes the pituitary to release LH and FSH, in a pulsatile fashion, with a periodicity of about 90 minutes for LH secretion and a less frequent pulse for FSH due to its longer half life (Reiter and Grumbach, 1982). FSH stimulates follicular development and a midcycle peak in LH secretion ruptures the mature follicle producing the corpus luteum. This results in

cyclical variation in ovarian steroid production, oestrogen being dominant during the follicular phase and progesterone during the luteal phase. As a result of this cyclical variation in ovarian steroid biosynthesis the endometrium undergoes proliferation followed by differentiation and finally menstruation. These changes are known as the menstrual cycle. However, because regular ovulation does not occur immediately following the menarche, these initial cycles are frequently anovulatory and the endometrium exhibits only a proliferative picture,

1.1.4. The Menstrual Cycle

a. Menstrual phase: During menstruation the surface epithelium of the endometrium begins to regenerate and regeneration is completed by the time overt menstrual loss ceases (Robertson, 1981). It is believed that the stromal cells by undergoing metaplasia contribute, along with nests of epithelial cells, to re-epithelialisation. The mature surface epithelium lining the uterine cavity resembles the glandular epithelium and a striking absence of any significant inflammatory response during this process of

regeneration is noted.

b. Proliferative phase: At the beginning of the proliferative phase the endometrial glands are straight, narrow and tubular in outline (figure 1). In response to rising oestrogen levels the glands proliferate and become more tortuous and slightly distended. The surface and glandular epithelial cells change from flattened or cuboidal to tall columnar cells and exhibit pseudostratification, and their nuclei migrate towards the gland lumen (figure 2). During this phase there is little activity within the stromal cells and because of their poor cytoplasmic development they appear as nuclei devoid of cytoplasm under light microscopy. However, during the mid to late proliferative phase the stroma becomes oedematous and the stromal cells appear spindle shaped (Robertson, 1981),

Secretory phase: The secretory phase of the cycle is conveniently divided into early (days 2-5), mid (days 6-9), and late (day 10 to menstruation) phases (day 0 = LH surge) (Johannison et al, 1982). By day two following ovulation the glands become more distended and pseudostratification is lost. Subnuclear vacuolation appears and the nuclei begin to migrate
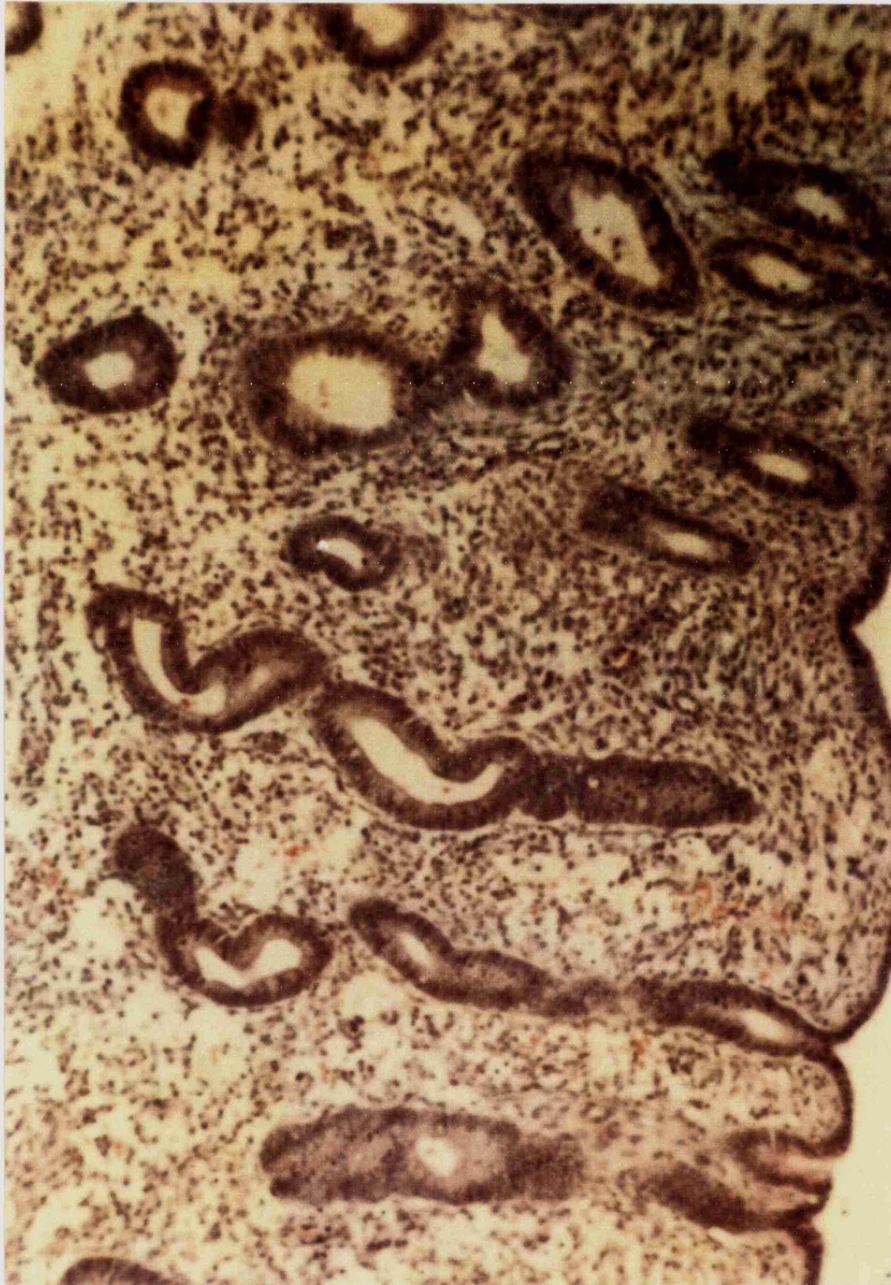
Figure 1. Early proliferative phase endometrium showing narrow, inactive tubular glands.
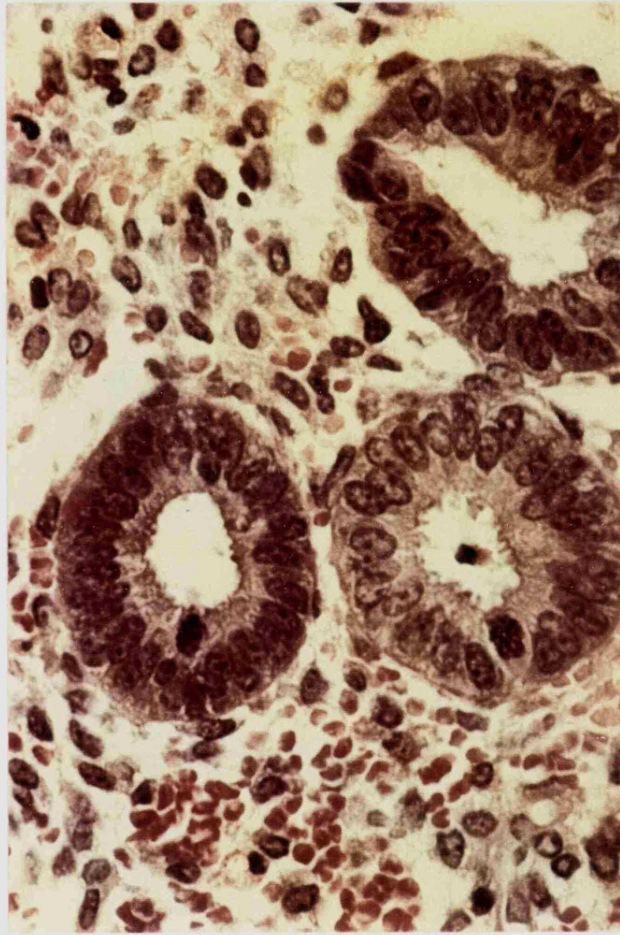
Figure 2. Late proliferative phase endometrium - glands exhibiting pseudostratification with loose oedematous stroma. Stromal cells devoid of cytoplasm.

towards the mid-region of the columnar cells (Figure 3). By days 3-4 the nucleus occupies the upper portion of the cell while the lower portion of the cell is occupied by secretions. By days 4-5 the secretions begin to stream past the nuclei and as supranuclear vacuolation develops, the nuclei become more basal in situation (Figure 4). By the seventh post-ovulatory day the cells have begun to discharge their secretions into the gland lumen. Stromal oedema is pronounced by day 8-9 and the glands are beginning to involute. By days 10-11 the glands begin to collapse and have a characteristic "saw tooth" appearance (Figure 5). Paradoxically during this time while the glands are undergoing involution, growth and development is occurring within the stroma. The vessels become more prominent and by day 10-11, prominent pre-decidual cells are seen forming perivascular cuffs. From day 12 onwards progressive predecidualisation of the upper layer of the endometrium occurs to form the zona compacta (Rock and Bartlett, 1937; Noyes et al, 1950; Figure 6). The zona compacta consists of prominent stromal cells with a relatively small amount of inactive glands. Underlying the zona compacta is the zona spongiosa consisting of prominent crenated glands
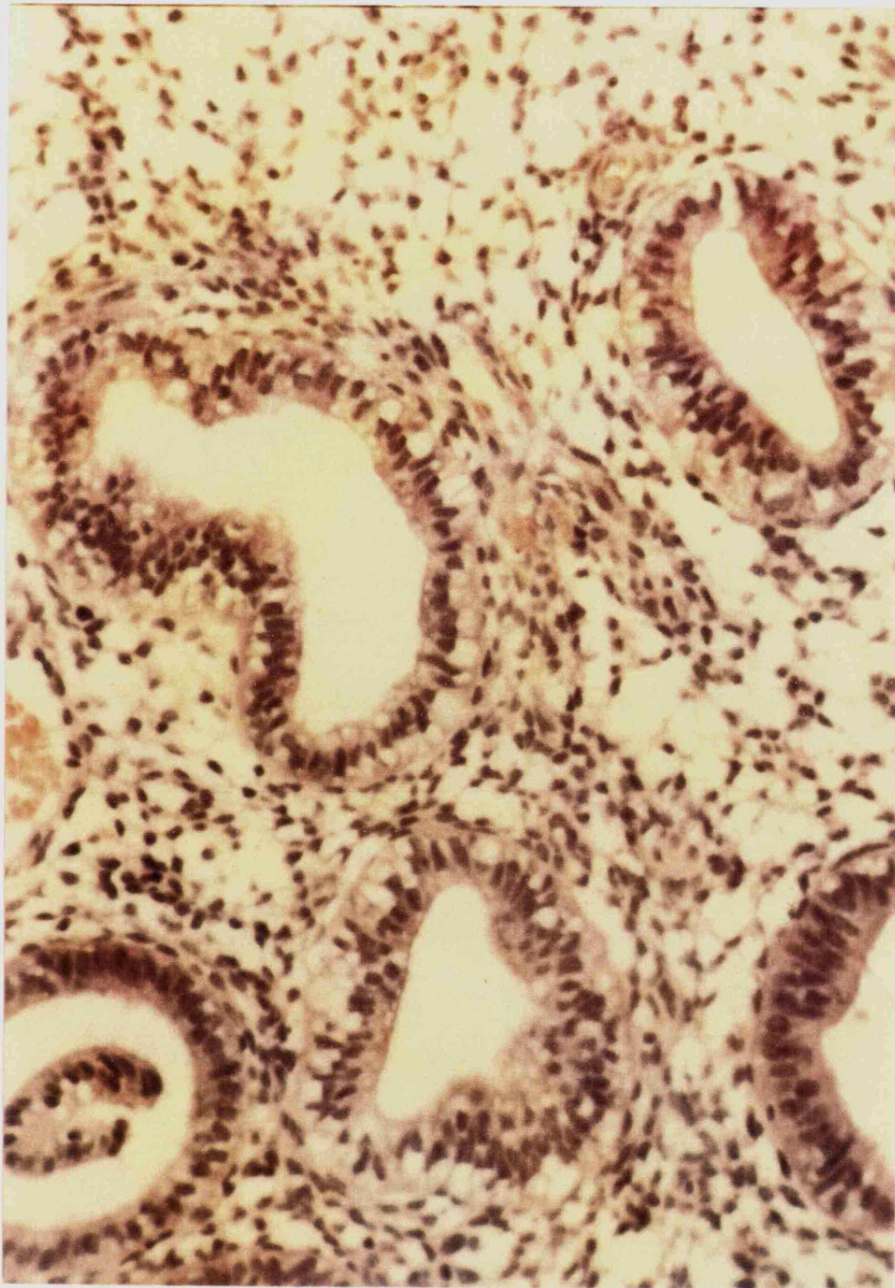
Figure 3. Early secretory phase endometrium − showing

subnuclear vacuolation.
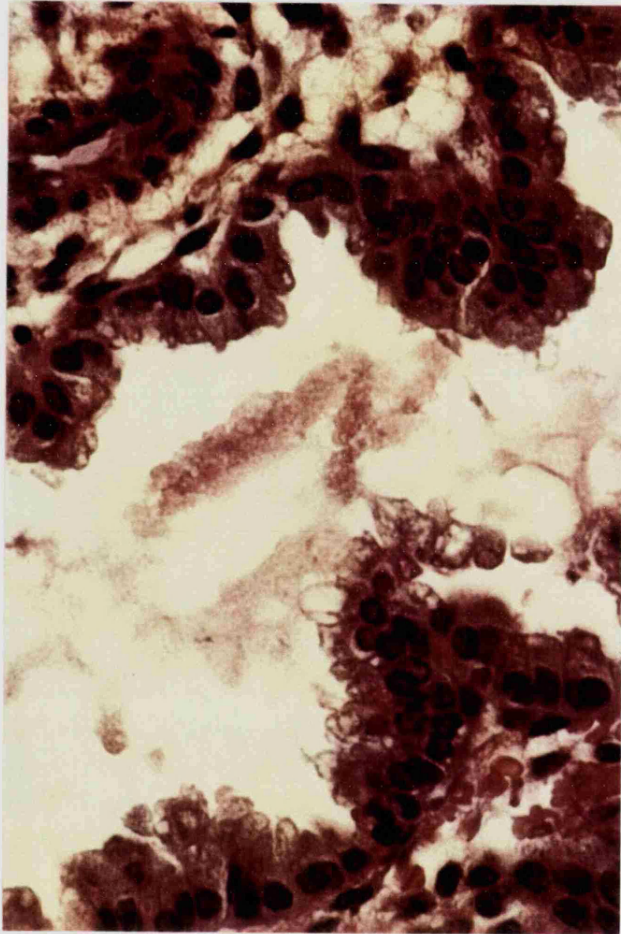
Figure 4. Mid-secretory phase endometrium - cells exhibiting basal nuclei with supranuclear vacuolation and active glandular secretions.
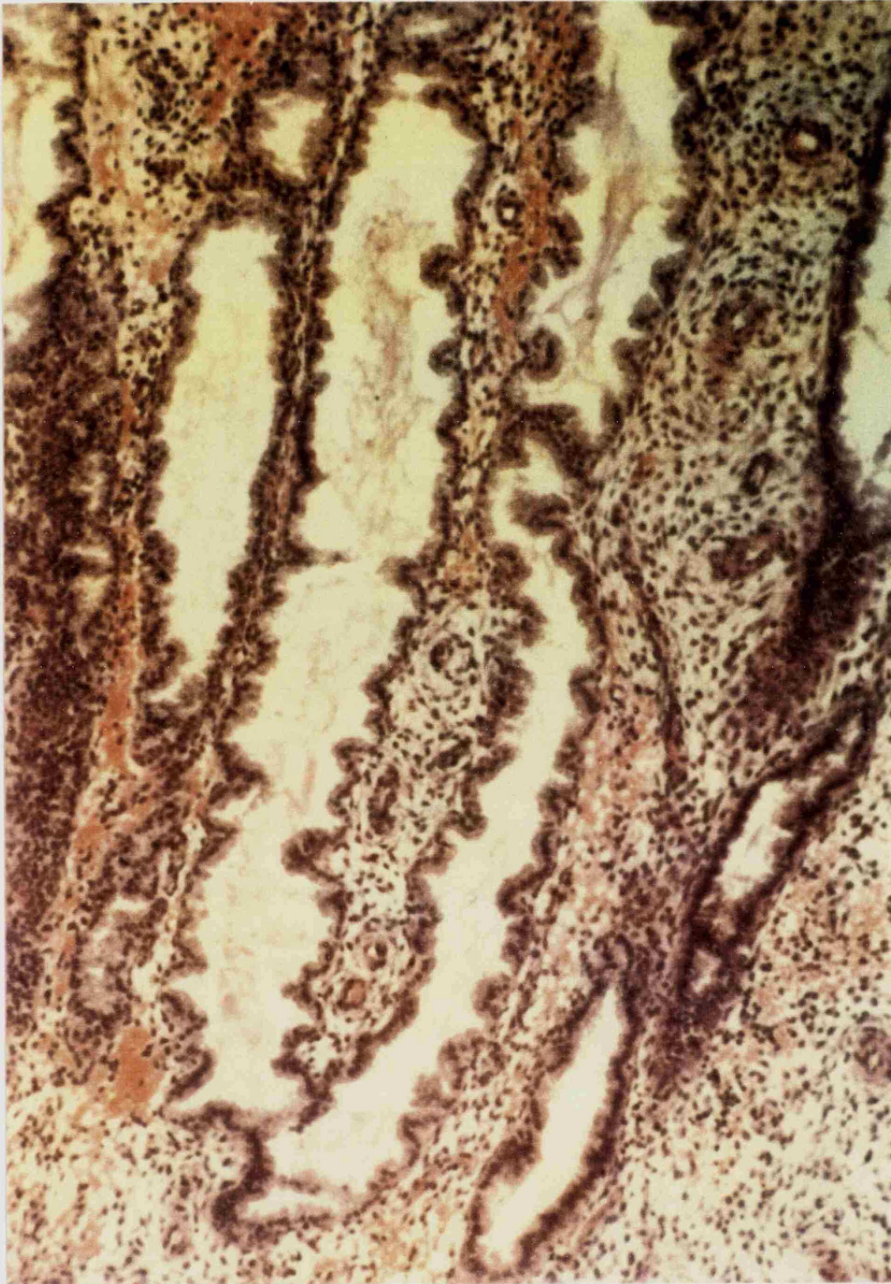
Figure 5 . Late secretory phase endometrium — showing exhausted 'saw tooth' glands.

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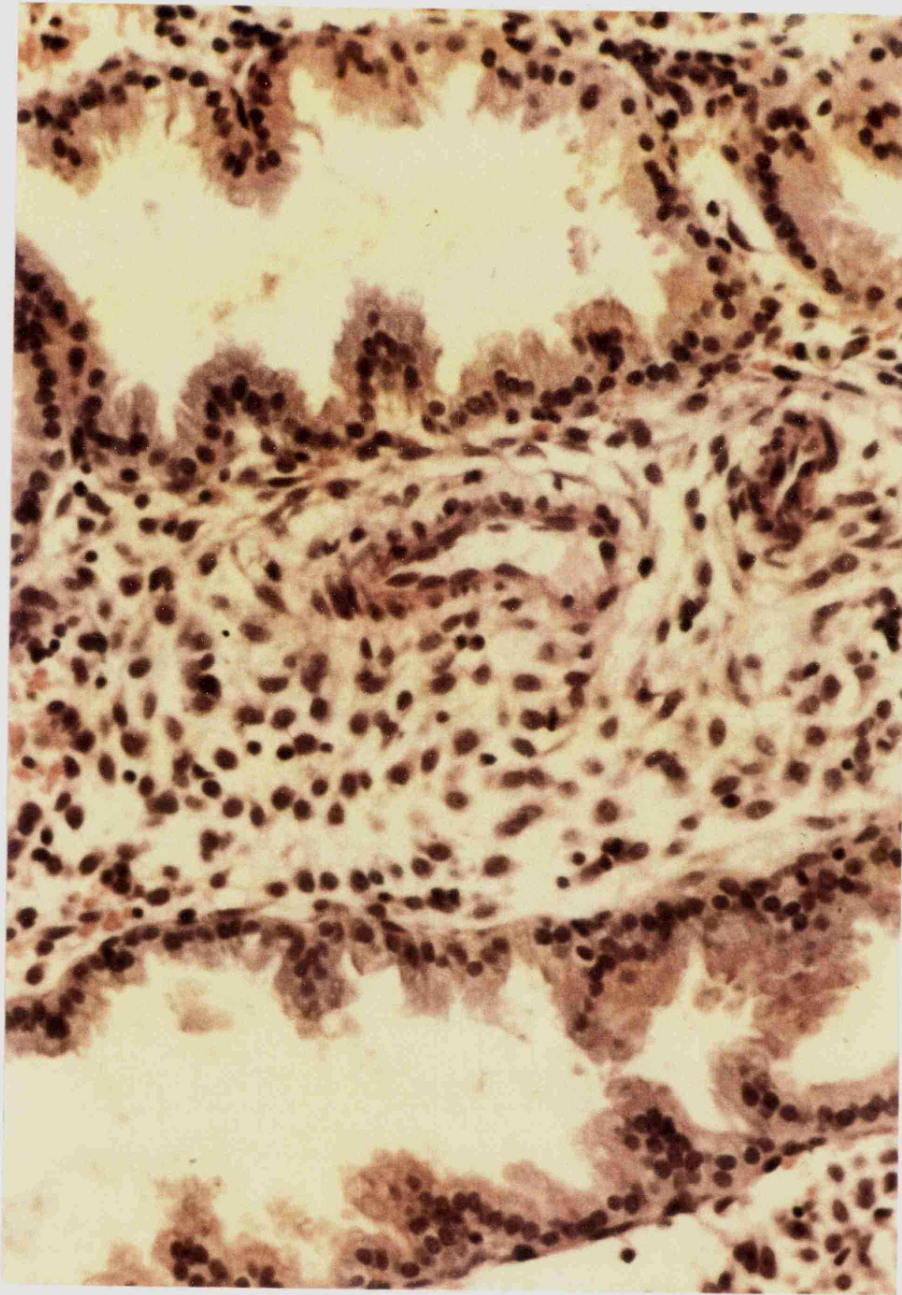
Figure 6. Late secretory phase endometrium - showing decidualisation within the stroma.

and beneath this layer is the zona basalis. It is this layer that is the target of endometrial ablation, since it comprises the layer of cells responsible for the cyclic regeneration of the other two layers, together known as the zona functionalis (Robertson, 1981). The stromal cells which become prominent during the secretory phase of the cycle are of mesenchymal origin and it is believed they may differentiate in two directions:

i. some enlarge to form the predecidual cells, and

ii. others contract to form small rounded cells known as granular endometrial stromal or K cells (Kornchen-zellin cells) (Weill, 1921; Numers 1953; Hamperl 1955; Hamperl and Hellweg 1958; Dallenbach-Hellweg, 1967). Although these cells have been identified during the proliferative phase, the largest numbers are found during the late secretory phase, localised around glands and arteries (Kazzazz, 1972). Later, Bulmer and Sunderland (1983) demonstrated that large numbers of cells within the decidua possess the human leucocyte common antigen and their distribution is similar to the endometrial granulocyte, suggesting that these cells are derived from the body's lymphocyte population and not differentiated stromal cells.

The precise histological mechanisms involved in endometrial regeneration will need careful consideration and scrutiny in the future, since the permanence of any cure effected by ablation will rely on such mechanisms not fulfilling their normal role.

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1.2 Menstruation

1.2.1. Introduction

Menstruation is a biological phenomenon which occurs only in humans and a very few other mammalian species (Fraser 1990b). Normal menstruation is uterine bleeding which results from cyclic degeneration of the zona functionalis of the endometrium, such that cellular debris and blood are shed and lost vaginally. Menstrual fluid consists of approximately 50% blood; the rest is lysed cells and transudate (Fraser 1985). Menstrual blood differs profoundly from peripheral blood, notably in respect of the virtual absence of fibrinogen: menstrual blood clots poorly. Current knowledge suggests that some clotting does occur within the uterine cavity, but very early degradation of fibrin polymers occurs (Sixma et al, 1980).

1.2.2. Mechanism Of Bleeding

The mechanism of endometrial shedding and menstrual blood loss was demonstrated by Markee (1940) in an intricate series of experiments where endometrium was transplanted into the anterior chamber of the eye in

monkeys.   Menstruation   occurs   when   serum   levels   of oestrogen   and   progesterone   simultaneously   fall   as   a result of involution of the corpus luteum, according to the following mechanism:

1.   Oestrogen   exposure   followed   by   oestrogen   and progesterone exposure secretory endometrium.

2.   Simultaneous oestrogen and progesterone withdrawal.

3.   Spiral   arteriole   vasoconstriction   ($PGF_{2\alpha}$ /?endothelin/local vasodilators)

4. Loss of tissue fluid: ischaemia.

5. Limited re-perfusion.

6. Triggering of:

*cell damage

*disruption of intercellular bonds

*loss of extracellular matrix

*limited blood clotting

*rapid fibrinolysis

*persistent predominant vasoconstriction

*limitation of loss of blood, plasma, fluid

*shedding of predecidualised layer

(prostaglandins,   leukotrienes   ,oxygen   radicles, perforins, platelet activating factor, interleukin 1β, tumour   necrosis   factor A,   lysosomes,   other   enzymes,

heparin).

7. Bleeding continues for 3-4 days.

8. Triggering of epithelial regeneration, (?oestrogen dependent growth factors).

(Fraser 1990b).

It is generally believed that an intense vasoconstriction at the endometrial-myometrial junction leads to tissue ischaemia, necrosis and eventually a histological picture similar to that of an acute inflammation, with migration of white blood cells into the tissues (Finn, 1986).

1.2.3. Haemostatic Mechanisms

Vascular Structure

Clearly, it would be inappropriate for physiological bleeding within the uterine cavity to occur in a fashion identical to that of pathological bleeding, because fibrin deposition and consequent scarring would lead to compromisation of the function of the uterine cavity. Apart from looking for differential concentrations of biological chemicals involved in bleeding and haemostasis in normal and menorrhagic

women, such as the prostaglandins, some workers have examined microvascular and clot formation morphologically.

Four possible factors are thought to play a role in endometrial haemostasis:

1. Myometrial constriction.

2. Vasoconstriction.

3. Tissue regeneration.

4. Haemostatic plug formation

Hourihan et al (1989) examined endometrial blood vessels in both normal women and those diagnosed as having dysfunctional uterine bleeding (DUB) both with the light and electron microscope. Vascular ultrastructure and haemostatic plug formation were examined from the late secretory phase throughout menstruation to day 9 of the proliferative phase of the cycle. They found no evidence of vascular anatomical defects in the DUB group. All arterioles examined in both groups were found to possess an intact intimal layer, and there was no significant difference in respect of cellular character (endothelial, smooth muscle or internal elastic luminal cells). However, the concentration of platelet plugs seen joining gaps

in the damaged endometrium of the DUB group was far
lower than that in the control group, suggesting that
haemostatic plug formation, or its provoking stimulus,
is critical in maintaining a normal rate of blood loss
at menstruation.

1.3. Dysfunctional Uterine Bleeding

1.3.1. Normal menstrual blood loss

Normal menstrual blood loss (MBL) is defined by Chamberlain (1981) as between 25-75ml, and losses of 125ml or more per cycle as "abnormal". Many methods have been used to determine the normal range of MBL, mostly by haemoglobin elution of sanitary pads, or, perhaps less accurately, by weighing pads before and after use (vanEijkeren et al 1986). Using the alkaline haematin method, where haemoglobin is converted to a haematin derivative that is measurable colorimetrically, the mean MBL in a population of normal women (n=476) was 43ml (Hallberg et al, 1966). The 95th centile for MBL was 76.4ml and 67% of women losing more than 80ml were anaemic. It is now widely accepted that the upper limit of normal is 80ml per cycle, therefore.

1.3.2. Abnormal menstrual blood loss

Abnormally heavy menstrual bleeding may be the

result of organic disease such as fibromyomas, intrauterine polyps or malignant neoplasia. Exclusion of organic disorder leads to a diagnosis of dysfunctional uterine bleeding (DUB). Although in a few cases, ovarian dysfunction such as prolongation of the luteal phase may be identified (Fraser et al 1973, vanLook

et al, 1977), generally speaking, no consistent abnormality of the hypothalamic-pituitary-ovarian axis has been identified (Cameron 1989). The endometrium itself has been the subject of intense study, however.

1.3.3. Oestrogen and progesterone receptors

There is some evidence that DUB may to some extent be explained by the observation that there may be a decreased ratio of total progesterone to total oestradiol receptor levels in DUB endometrium. Gorodeski et al (1986) measured receptor levels in 22 women suffering from DUB and compared them to those found in the endometria of subjects matched with respect to age, history, light and electron microscopic appearance and dating of the endometria. A wide range of both progesterone and oestradiol levels was found in both groups, but

there was a statistically significant difference between the two groups in that the DUB group had relatively low ratios of progesterone to oestradiol receptors. It may therefore be the case that DUB endometrium is especially sensitive to the growth stimulating properties of oestrogens.

1.3.4. Prostaglandins

Prostaglandins (PG's) are complex molecules biosynthesised from the essential fatty acid, arachidonic acid.

They have been identified in a large range of tissues including endometrium, and act as 'local mediators' at

the tissue level, of a diverse number of biological functions. Within the endometrium, the principle effects of the PG's involved seem to be vasoconstriction and vasodilatation.

PG's themselves are not stored in tissues, but are synthesised on an "as needed" basis from stored precursors. Arachidonic acid is converted to the

cyclic endoperoxidases PGG_2 and PGH_2. These unstable intermediates are converted rapidly to either PGD_2, PGE_2, or $PGF_{2\alpha}$, or via prostacyclin synthetase or thromboxane to thromboxane (TX) A_2 and prostacyclin (PGI_2). These two compounds are themselves unstable, and are subsequently converted to TXB_2 and $6oxoPGF_{1\alpha}$. The physiological response resulting from activation of the synthetic cascade depends upon the relative concentrations of each of the active substances finally produced. In the case of the endometrium, the major effects are upon vasculature and muscle:

TXA_2: vasoconstrictor, platelet aggregation stimulator

PGI_2: vasodilator, platelet aggregation inhibitor

$PGF_{2\alpha}$: vasoconstrictor, myometrial contraction stimulator

PGE_2: vasodilator (less potent than prostacyclin) (Griglewski et al, 1976, Pickles et al, 1965, Chan and Hill, 1978, Lumsden et al, 1983).

The major endometrial PG's are PGE_2 and $PGF_{2\alpha}$. Their concentrations vary according to the phase of the cycle: low in the proliferative phase,

rising during the second half of the cycle (Maathuis and Kelly, 1978, Rosing and Olund, 1989). Some PGD_2 and $6oxoPGF_{1\alpha}$ are also found, but in much smaller concentrations.

Increased concentrations of PGE_2 and $PGF_{2\alpha}$ have been reported throughout the menstrual cycle in women complaining of DUB, but this was not objectively demonstrated by measuring MBL (Willman et al, 1976). However, Smith et al (1981, 1982) measured MBL using the alkaline haematin method to confirm heavy loss, and found an increase in PG concentrations in the endometrium of women suffering both ovulatory and anovulatory menorrhagia, and moreover, there was a significant increased ratio of PGE_2 to $PGF_{2\alpha}$ (ie. a shift from vasoconstriction to vasodilatation). Further studies have confirmed that there are increased levels of "total" PG's (Cameron et al, 1987, Adelantado et al, 1988).

However, Peek et al (1987) have pointed out that PG concentrations vary in tissues according to the method used to collect the samples. It is therefore important to be aware of the exact

methodology employed before comparing results from
different studies, since measured PG levels are
raised by trauma to the endometrium.

1.3.5. The fibrinolytic system

The fibrinolytic system operating within the
uterus seems to be very much more active in DUB
compared to controls (Dockeray et al, 1986).
Plasminogen activators have been shown to be
significantly higher in women with heavy menstrual
bleeding, although the endometrium was hyperplas-
tic (Soszka and Olszweski, 1986). The contention
that an abnormality of the fibrinolytic system is
implicated in menorrhagia is further supported by
the fact that antifibrinolytic agents such as
tranexamic acid are effective in the management of
DUB(Westrom and Bengtsson, 1970). The concept of
"activation" of menstrual blood inside the uterus
is an accurate one, since platelets fail to
aggregate in vitro (Rees et al, 1984). Moreover,
menstrual blood contains virtually no active
plasmin, but high levels of tissue plasminogen
activator, fibrinogen degradation products (FDP's)

and plasmin activator complexes (Williams *et al*,
1984).

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1.4 The Treatment Of Menorrhagia

1.4.1. Introduction

The definition of 'menorrhagia' is excessively heavy menstrual bleeding. Although often used synonymously with DUB, the two terms differ in that menorrhagia may have an underlying identifiable cause, such as fibroids or polyps. Once underlying pathology is excluded, a diagnosis of DUB may then be made.

Attempts in the past to objectively assess blood loss volume in women complaining of menorrhagia by measuring haemoglobin or previously injected radio-isotopes in used sanitary pads have universally concluded that approximately 50% or more are not actually bleeding more than a normal amount Hallberg et al, 1966,
Fraser et al, 1985). However, such studies suffer from potential inaccuracies: up to 60% of MBL may occur at the time of micturition, and hence not measured on pads (Corstens et al, 1989). Any clot lost at the time of pad change will similarly not be taken into account. An alternative technique

to measure MBL using radioactive iron injection and whole body counting (Warner, 1973) does not suffer these disadvantages. Using this technique, several workers have confirmed excessive bleeding in the majority of menorrhagic patients studied (Price et al, 1964, Holt et al, 1967, Flach and Deckart, 1977, Phipps et al, 1991).

It has been argued by Short (1976) and others that regular menstruation is an artefact of western modern society. In hunter-gatherer societies, most women enter menarche late, mother several pregnancies and lactate for prolonged periods of time. Under these circumstances, most women will experience 50-100 menstrual cycles, whereas in the west, most women have 400 or more. There is a corresponding increased incidence of gynaecological problems in western women partly as a consequence of prolonged 'exposure' to the uninterrupted menstrual cycle; dysmenorrhoea, premenstrual syndrome, menorrhagia, fibroids, endometriosis and uterine and ovarian malignancies.

Once organic pathology has been excluded by careful clinical examination, diagnostic hysteroscopy and endometrial biopsy, DUB may be treated either medically or surgically.

1.4.2. Medical treatment

1.4.2.1. Radiotherapy

Packing of the uterine cavity with radioactive sources and external beam radiotherapy has now fallen into almost complete disuse because of the potential risk of oncogenesis. Although packing the cavity was an attempt at endometrial ablation, it seems likely that in some cases at least radiation penetrated out to the ovaries and exerted its amenorrhoiec effect by stopping ovarian steroid production. Rarely, in cases of intractable bleeding, radiation menopause is occasionally employed, but with the advent of endometrial ablation, this is likely to become even rarer.

1.4.2.2. Hormonal treatments

i. Combined oral contraceptives

These have been shown to substantially reduce measured MBL in women complaining of menorrhagia (Chamberlain, 1981). Women using oral contraceptives are less likely to complain of irregular or heavy bleeding than controls (Royal College General Practitioners, 1974). Women with either ovulatory or anovulatory DUB may benefit from oral contraceptives, but other factors may make them unsuitable for treatment, such as smoking, age over 40 years, family history of cardiovascular disease, diabetes or hyperlipidaemia.

ii. Progestogens

Progestogens given alone during the second half of the cycle augment the secretory effect on the endometrium of endogenous progesterone. For example, norethisterone 10mg a day or medroxy-progesterone acetate (MPA) 20-30mg a day in most patients from day 12-15 to day 25-26 will produce predictable bleeding (Fraser, 1989). Women with

excessive early oestrogen secretion may need longer exposure , up to three weeks out of four.

Depot injections such as Depoprovera (Upjohn) have been used, but irregular bleeding is a problem which becomes progressively more troublesome as levels of progestogen fall off.

iii. Progestogen-releasing IUCD's

Luukkainen et al (1990) report the use of a levonorgestrel-releasing IUCD over 15 years in some 8000 women years. They report a 95% 'cure rate' in menorrhagic women, with a low infection rate and good contraception. MBL was measured in 20 patients before and after Progestasert treatment, and was significantly reduced by 86% by three months and by 97% after 12 months (Anderson and Rybo, 1990). This form of treatment avoids the systemic side effects of progestogens such as weight gain and depression, and may therefore be a safe and effective means of treating DUB. The device is similar to the Nova-T IUCD and bears 46mg of levonorgestrel, released at the rate of approximately 20 micrograms per 24 hours.

1.4.2.3. Danazol

Danazol at the relatively low dose of 200mg a day
is highly effective in the treatment of DUB , and
has been shown to be superior to mefanamic acid in
a study of 40 patients where MBL was measured
objectively (Dockeray et al, 1989).   Unfortunate-
ly, danazol therapy is known to reduce high
density lipoprotein levels, and the androgenic
effects tend for poor patient compliance   if
therapy is prolonged.   Cameron et al   (1987a)
compared danazol to mefanamic acid, norethisterone
and Progestasert with respect to MBL   and
endometrial PG concentrations. They found that
danazol 200mg a day was equally effective as the
IUCD and mefanamic acid, but came to   no
significant conclusions regarding effect   on
endometrial PG concentrations.

The mode of action of danazol is complex, but it
seems likely that a significant part of its
pharmacology relies on acting as an oestrogen
receptor block at the pituitary level, reducing
gonadotrophin output. Fedele et   al   (1990)

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examined endometrial biopsies after danazol therapy by light and electron microscopy. Six morphometric indices were evaluated. Danazol produced a progestational effect on endometrial glands and stroma associated with marked hypotrophy of the mucosa.

1.4.2.4. Prostaglandin inhibitors.

The logical use of PG inhibitors to reduce MBL has already been discussed (section 1.3.4.). Several groups of drugs reduce PG synthesis, and these act mainly by inhibiting the cyclo-oxygenase system (Fraser, 1989). There is now an extensive literature demonstrating that some of these agents may produce a substantial reduction in MBL in a high proportion of women with DUB. The most commonly used compound is mefanamic acid, 500mg three or four times a day taken during menstrua-tion. Cameron et al (1990) objectively demonstrated a significant reduction in MBL both with mefanamic acid and norethisterone, and both compounds were similarly effective. However 52-67% of the women treated still complained of

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menorrhagia at 12 month follow up. PG synthesis inhibitors reduce MBL on average by between 30 and 45% (Hall et al, 1987, Anderson et al, 1976, Andersch et al, 1988).

Vargyas et al (1987) looked at the effect on objectively measured MBL of meclofenamate sodium, a compound less popular in the UK. They found that in 29 patients treated for two or more months, MBL was reduced on average from 141.6ml to 69.0ml, with a 'cure rate' (ie. the patient content) of 26/29.

1.4.2.5. LHRH analogues

Repetitive LHRH analogue dosing induces a down regulation of gonadotrophin secretion and is effective in decreasing serum oestradiol levels near or into the menopausal range (Lemay and Dewailly, 1989). Several LHRH analogues can induce reversible pseudo-menopause for the treatment of sex steroid dependant gynaecological problems such as endometriosis, fibroids and polycystic ovary disease (Lemay et al, 1986, Maheux et al, 1985). Their main side effects are

related to oestrogen deprivation, Vasomotor symptoms are said to be well tolerated, and adverse alterations of lipoprotein balance do not seem to be a problem.. There is also an increased urinary excretion of calcium/creatinine and hydroxyproline/creatinine ratios and a progressive loss of bone mineral content (Steingold et al,1987). However, this is reversible once therapy is withdrawn.

Intranasal buserilin (ICI) has been used both alone and in combination with MPA (Lemay and Dewailly, 1989) at a dose of 400-600 micrograms daily to good effect in patients with DUB, although no objective studies of MBL were performed.

Seven healthy volunteers were given buserilin for 2-17 months and endometrial biopsies taken. Circulating oestradiol levels had fallen in all cases, and electron microscopic examination of the endometria showed inactive or weak proliferative pattern, with no signs of hyperplasia (Lundkvist and Bergquist, 1986), a finding confirmed by

Fedele et al (1990).

Reduction in measured endometrial PG concentrations has been demonstrated repeatedly, (Tsang et al, 1987, Makarainen and Ylikorkala, 1986).

1.4.2.6. Fibrinolytic inhibitors

Several investigators have reported significant reductions in MBL after treatment with epsilon-amino-caproic acid (EACA) and tranexamic acid (AMCA) (Westrom and Bengtsson, 1970, Kassonde and Bonnar, 1975). Reduction in loss by about 50% is repeatedly documented, but large doses of compound are required, eg. AMCA 1g six hourly for several days. These drugs are potent inhibitors of the conversion of plasminogen to plasmin, and have few side effects (mild nausea and vomiting). Fears concerning thrombus production seem groundless.

1.4.2.7. Gestrinone

Gestrinone (Roussel) is a 19-nor-testosterone derivative that is an anti-progesterone and anti-oestrogen with some androgenic activity. It

interacts with hypothalamic and pituitary steroid receptors to decrease the circulating levels of FSH and LH. Turnbull and Rees (1990) have shown a measured reduction in MBL in a double blind randomised study in 19 women with DUB, performed in a cross-over fashion. Whereas placebo had no effect on MBL, during gestrinone therapy 10/19 became amenorrhoiec, 5/19 showed a significant reduction in MBL, and 4/19 were unchanged. In three of the non-responders, submucous fibroids were later found. Further work is needed for this relatively new compound, which because of its long half life only has to be given twice weekly. Long term studies of side effects, especially on the lipoprotein balance need careful consideration.

1.4.3. Surgical treatment

1.4.3.1. Dilatation and Curettage

Most authorities would now accept that this is essentially a diagnostic procedure, and in cases of true DUB has no therapeutic value. Of course, if there are polyps within the uterus, the patient may well be cured. It has been argued that dilatation and curettage (D&C) is an inadequate diagnostic tool without hysteroscopy since it may be the case that up to 10% of intrauterine lesions may be missed by a single curettage (Hamou, 1988). Although in the past claims have been made for the long term benefit of D&C for DUB, objective studies of MBL before and after D&C have failed to show any reduction in loss except for the first cycle (Haynes et al, 1977).

1.4.3.2. Hysterectomy

When considering any method of treating functional menorrhagia, it is important to bear in mind that existing traditional methods are both costly and

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potentially dangerous.

If medical treatment with either progestogens, anti-oestrogens or fibrinolysis inhibitors fail, the most commonly employed next step is hysterectomy. Indeed, the most frequent indication for hysterectomy is primary dysfunctional bleeding when the uterus is histologically normal (Cole and Berlin 1977). Although this course of action offers a permanent cure, there are serious side effects. The mortality rate directly attributed to hysterectomy is widely reported as being between 0.05-.2 per cent (Sharp and Jordan 1987), but there is potentially considerable morbidity if complications occur. The most common are those which follow any major surgical procedure (infection and haemorrhage), but there are special risks attached to hysterectomy. Injury to the urinary tract, especially the ureters, has been reported to be as high as 1.5 per cent (Daly and Higgins 1988). Others include psychological damage (van Emden and van Tergouw 1987), dysparenia ('ovarian residual

syndrome'), and incontinence.

Vaginal Hysterectomy

This is a safer procedure in terms of operative and post operative complication rate, both being approximately one third to one half that of abdominal hysterectomy. In trained hands vaginal hysterectomy without prolapse (and therefore without the need for anterior or posterior repair) is safe and quick, but there is reluctance amongst some gynaecologists to perform the operation unless there is appreciable descent. This seems largely to be a function of training and experience.

Abdominal hysterectomy

This is the preferred route if there is significant uterine enlargement. The decision on route based on uterine size is entirely at the discretion of the operator for reasons given above. Some surgeons will remove a 12 week pregnancy size uterus without difficulty after bisection, whilst others would prefer to operate abdominally under almost all situations.

The incidence of all major complications after abdominal hysterectomy, especially urinary tract injury, is much higher than that encountered after a vaginal operation (Cole and Berlin, 1987). The advantage of the abdominal route is that the whole pelvis and if necessary, the abdomen, may be examined at the same time.

In conclusion, somewhere between the two extreme views of the acceptability of liberally offered hysterectomy for DUB, there should be a balanced view, although a great deal of personal opinion and ideology contribute to affecting which argument the gynaecologist favours.

Those in favour of the liberal use of hysterectomy, quoting low complication rates in personal series, must bear in mind that others may not enjoy the same success rate. The statistic quoted by Daly and Higgins (1988) concerning urinary tract injury (1.5 %) is often met with incredulity or frank disbelief. Studd (1989), and others, take a different view,

however. He points out that a substantial proportion of patients will be exposed for significant periods of time to medical therapy in the hope that the menopause will supervene, only to fail to respond and eventually undergo hysterectomy anyway. Moreover, patients who do not have a uterus are considered safe for the administration of unopposed oestrogen hormone replacement therapy (HRT) by many authorities, and enjoy the benefits of both avoiding the unpleasant side effects of progestogens and the reappearance of 'periods'. Furthermore, in advocating the more liberal use of bilateral oophorectomy at the same time, he sites those cases (anecdotally) where total hysterectomy alone is followed some years later by ovarian residual pain, where further (potentially difficult) major surgery is needed.

In favour of hysterectomy for DUB, Gath _et al_ (1982) showed that women complaining of menorrhagia were more likely to have a history of psychological disturbance, which improved after hysterectomy (using standard psychometric testing). However, it is difficult to say which of

the two factors precipitated the other. As Studd

points out: "Is it not likely that two or more

weeks of bleeding, pain, menstrual headaches and

premenstrual syndrome each month are the cause of

depression rather than the effect?" (1989, p.

417).

1.5 - Endometrial Ablation

1.5.1. Introduction

Treatment of abnormal uterine bleeding by destruction of the endometrium is by no means a novel concept (<u>vide infra</u>). However, attempts in the past have been disappointing, although the latest attempts using either the laser or electrodiathermy under direct hysteroscopic vision have met with some success. The aim of the project recorded here was to test the feasibility of destroying the endometrium safely by heating to so-called 'hyperthermic' temperature, ie. approximately 44-55 degrees Celsius for an appropriate length of time. There is a vast literature on the subject of hyperthermia, which is more usually associated with the treatment of malignant disease. This project therefore represents a collaboration between gynaecology, engineering, physics and oncological technology.

The ultimate aim of this work was to create a technique that would save patients from hysterectomy, and convert a long stay in hospital

and convalescence to a simple 'day case' procedure with all the advantages inherent in day case care (Loffer 1987a).

Over the years several attempts have been made to render the endometrium inactive without actually removing the uterus. Asherman described the syndrome of amenorrhoea after deep curettage in the post-pregnant uterus in 1948. It soon occurred to many workers that if it were possible to therapeutically reproduce this phenomenon in the non-post pregnant uterus, then this might offer some help to menorrhagic patients. Many early attempts used hypertonic or toxic substances such as quinacrine, oxalic acid, cyanoacry-late ester ('superglue'), paraformaldehyde or silicone rubber instilled or injected into the endometrium, but all of these failed (Goldrath 1987a). Intracavity radium has been tried and although partially successful, has been abandoned because of the risk of carcinogenesis. The application of superheated steam was unsuccessful (Falconer 1947), and in 1989 was reported to be responsible for two severe injuries, where one patient died (Hardt and Genz, 1989) from 'atmocausis' of the endometrium.

1.5.2. Cryosurgery

1.5.2.1. Introduction

The application of profoundly cold probes to the endometrium for the purpose of ablation was reported first by Cahan and Brockunier (1971). Considerable experience has been gained in using this technique, either with liquid nitrogen as the freezing medium (Cahan and Brockunier), or the halogenated hydrocarbon 'Freon' (Droegemueller et al 1971). These represented the first successful attempts to destroy the endometrium for the treatment of intractable menorrhagia using physical means. Probes were developed which conducted the coolant within the probe itself, cooling the endometrium to between -40 and -80 degrees Celsius. Histological examination of hysterectomy specimens 3-4 weeks later revealed destruction of the endometrium to a depth of 'ten per cent of the myometrial thickness' (Cahan and Brockunier 197|). Unfortunately, large areas of

the cornua were left intact.

1.5.2.2. Clinical performance

Six patients were originally reported, and all of these were reported to have some degree of reduction in menstrual flow. Measurement of menstrual flow was not performed, however, and no patient became amenorrhoeic.

The probes used were of relatively small diameter (6mm), and had been applied to different areas within the uterine cavity in order to coagulate ('congelate') an adequate area of endometrium due to the uneven shape of the cavity, especially proximally. Thus the technique involved multiple placings, blindly, of a rather pointed probe within the uterus, capable of delivering histotoxic temperature drops. There was no way of ensuring that any single area within the cavity did not receive two or even three exposures to histotoxic effects at the treatment 'zone' overlap. Although perforation of the uterus and exposure of abdominal contents to the cryoprobe seems a distinct possibility, this was not reported.

1.5.2.3. Safety testing

Cahan and his colleagues did perform inter-operative thermometry at abdominal hysterectomy to monitor the effects of the cryoprobe, by placing thermocouples within the substance of the myometrium and at the serosal surface. They found, however, that the appearance of frost on the serosa was a necessary accompaniment to adequate endometrial congelation.

These experiments with liquid nitrogen represented the first partially successful attempts at ablation of the whole endometrium simultaneously, and to this extent Cahan's technique is along similar lines to RaFEA. The critical differences are firstly that the cryoprobe had to be moved during treatment leading to potential problems already outlined, and secondly the cryo method relied upon simple thermal (or 'cold') conduction to achieve adequate depth of destruction. Penetration would therefore be expected to be somewhat erratic, with potential for both 'missed' areas and over-penetration. Since RaFEA relies on the physical attributes of an electric field (vide infra), such limitations are, theoretically at

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least, reduced or absent.

1.5.2.4. Complications

Patients treated with cryosurgery are prone to pyometra and fistula formation (Droegemueller <u>et</u> <u>al</u>), presumably due to destruction of the full thickness of the uterus in places. The method has now been largely abandoned in favour of more recent methods of local ablation.

1.5.3. Hysteroscopic Nd-YAG Laser Therapy

1.5.3.1. Introduction

The rapid advances in medical laser technology in the late 1970s and early 1980s saw the advent of the neodymium-yttrium-aluminium-garnet (Nd-YAG) laser. Unlike the Argon or carbon dioxide surgical lasers, the Nd-YAG laser is not well absorbed by either water or haemoglobin. Thus the instantaneous vaporisation of tissue seen with the former two is not seen with the Nd-YAG device. This is principally because the wavelength of the Nd-YAG is $1.0\mu m$ (Argon $0.5\mu m$, carbon dioxide $10.6\mu m$), giving an extinction length ('thickness' of a water target required to absorb 90 per cent

of incident energy) of 60mm compared to 0.3mm for carbon dioxide. Thus Nd-YAG tissue penetration is much further and diffuse by comparison.

Nd-YAG laser beams are capable of being conducted and directed along a fibre-optic medium, and thus be applied to anywhere within the body that is capable of examination by an endoscope. Fibre optic conducting leads are placed along the operating hysteroscope channel, and contact with the endometrial cavity under direct vision. This is the first major difference from the cryosurgical technique - the ablative process is observable by the surgeon. It is therefore possible to ensure accurate application of the destructive energy to target tissue and provided there is a visible indication of destructive effect, control dose.

1.5.3.2. Clinical Performance

The most effective method of delivering the histotoxic energy appears to be systematic 'blanching' (coagulation) of the endometrium by

application of the laser either from the exposed
end of the fibre optic cable, or through the
medium of a sapphire tip (Lomano, 1988), not in
direct contact with tissue, at 40-50W incident
power. Using this technique in 30 patients,
Lomano found that 65 per cent became amenorrhoiec,
22 per cent oligomenorrhoiec, and 13 per cent were
the same. No serious side effects were observed,
and patients experienced only mild discomfort.

Loffer (1987b) reported 36 patients treated using
the non-touch Nd-YAG laser technique, and reported
'excellent results' in 93.9 per cent of 33
patients in whom surgery was uncomplicated (in
three there were technical difficulties).
Amenorrhoea was achieved in 11 patients,
oligomenorrhoea in 13 patients, and a reduction in
flow to 'normal' in seven patients. Again, no
objective measurement of blood flow was performed.

These results are concordant with those of
Dequesne (1986), Cornier (1986), and Bent and
Ostergard (1990).

1.5.3.3. Safety Testing

In vitro testing with regard to safety has been carried out by Goldrath (1981, 1987) and his co-workers, who looked at in vitro penetration of heat outside the uterus when the laser was incident upon the endometrium. In a water bath at 37 degrees a 40W Nd-YAG laser was aimed at the endometrium, and the temperature at 10mm from the exposed endometrial surface was recorded using an accurate thermocouple device. He found that there was no significant rise in temperature at exposure times likely to be encountered during clinical treatment. Moreover, he pointed out that this was a 'worst case' experiment, since the protective (of the outer uterus and pelvic contents) cooling blood supply was absent. No attempt was made to study the effects of laser light or thermal energy thereby generated upon the blood flowing through the uterus during treatment. However, there has been no recorded incident in the available literature to date of systemic disorder related to haematological damage. Rosenberg et al examined the effect of the Nd-YAG laser in the endometrial cavity in rabbits (1990), and compared it to the

holmium laser. Although the latter seemed to ablate more effectively, adequate endometrial destruction was observed using the Nd-YAG without excessive myometrial over-penetration.

Despite the high cost, lengthy anaesthetic and specialist skill required, the Nd-YAG laser technique is an effective one, and is particularly suited to those patients who are unsuitable for hysterectomy because of technical difficulty (obesity, previous surgery), poor operative risk, or those who are strongly motivated to avoid excision surgery.

However, it is noteworthy that there has yet to be a study where the efficacy of the technique has been demonstrated objectively in terms of reduced menstrual blood flow. In addition, Baggish and Baltoyannis (1988) point out that long-term follow up data is scant, and there is no pathological specimen at the end of the operation. The latter criticism applies to any endometrial ablative procedure, however.

1.5.3.4. Complications

Nd-YAG laser endometrial ablation complications are of three types. Penetration of the uterine wall and damage to non-target tissues such as bowel or urinary tract, fluid overload problems and electrolyte disturbance, and gas embolism.

There are a number of anecdotal examples of injury to bladder, ureters, bowel and extrauterine blood vessels, but reporting has, on the whole been scant. Morrison et al report a biochemical study of 12 women who had undergone laser ablation, and measured a significant rise in central venous pressure and serum chloride and a significant drop in serum protein concentration and haematocrit. In one case, this was considered 'excessive', but the patient suffered no medium or long term ill-effects. However, Feinberg et al report a case of significant pulmonary oedema after laser therapy (1989). More alarmingly, there has been at least one case of fatal air embolism after gas was admitted to the endometrial cavity during laser ablation (Challener and Kaufman, 1990).

1.5.4. The Hystero-Resectoscope

1.5.4.1. Introduction

More recently, a device resembling a miniature urological resectoscope (more usually used for transurethral resection of prostate and urinary bladder tumours) has been devised and used to good effect, although the technique is still in the early stages of development. A wide-bore operating hysteroscope with triple channels is fitted with the resectoscope device and an inlet and outlet line for a continuous flow of distension medium. The resectoscope consists of a cutting diathermy loop on the end of an insulated rod which slides back and forth when the trigger is operated. Since the energised loop is mounted at 90 degrees to the rod, a 'sweeping' action is possible to excise the endometrium in strips. The loop is energised by a standard diathermy unit with high frequency current at 500kHz at around 100W incident power. The return side of the circuit is provided by a low resistance zero capacitance external electrode. At this range of frequency, current flows mainly resistively, with little capacitance conduction. Where the loop is

in contact with tissue thermal energy is produced, and a combined cutting/coagulation effect is achieved. Because the hysteroscope is of wide diameter, an excellent view of the endometrial cavity is obtained. Continuous irrigation of the operative site maintains a clear view. The distension medium must be non-conducting otherwise the loop is shorted out, and no diathermy effect is achieved. Commonly, a 1 per cent glycine solution is used.

1.5.4.2. Clinical Performance

DeCherney reported the technique in 1983 and 1987, as did Hamou in 1988 (150 patients). Of these, 70% were 'improved', but again no objective test of blood loss was performed. Later, Magos (1989a) reported the technique, initially in 12 patients but later in a larger series of over 100 (1990). The use of the resectoscope under local sedation has been reported (Magos et al, 1989b).

1.5.4.3. Safety Testing

A number of workers have looked at diathermy

penetration into tissue both in animals _in vivo_ (Riedel _et al_, 1990), and _in vitro_ (Indman and Soderstrom, 1990). Indman and Soderstrom point out that tissue damage from diathermy is not immediately apparent visually, and several days must elapse before the true extent of the damage may be seen. In an effort to attempt a more accurate prediction of tissue damage, histochemical chemical studies have been performed to look at cellular enzyme survival/denaturation after exposure to thermal insults. Care must be exercised in interpreting this type of study, since critical cellular proteins are not denatured until 60 degrees is achieved intracellularly (Gorisch and Bergen, 1982, McKenzie, 1983). Tissue damage due to hyperthermia effects (_vide infra_) will therefore not be observed. However, in procedures where point exposure to thermal injury is brief, such techniques are likely to at least reasonably well reflect the 'true' situation, since hyperthermia effects are likely to be minimal (unlike the case with RF ablation). Further testing _in vivo_ is needed, especially in view of the fact that the myometrium is

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excessively thin at the cornua, isthmus and cervix.

1.5.4.4. Complications

The technique is faster than the Nd-YAG method (approximately 50 minutes), but has yet to be fully assessed. Over-penetration of the myometrium and consequent bleeding is a recognised complication. Between early 1990 and mid 1991 there were at least three deaths due to large blood vessel resection, the loss of a leg, and several cases of both bladder and bowel injury due to endometrial resection (RCOG Committee On Endometrial Ablation, Personal Communication). There have also been a number of cases of both uni- and bilateral ureteric resection. Sub-lethal air embolism has also been reported when gas has been allowed to enter the resected cavity under pressure (Wood and Roberts, 1990). Also of concern is the potentially fatal effects of excessive intravasation of the distending medium, glycine. The aim of the technique is to resect to a depth of approximately 7mm. At 10mm significant vascularisation is encountered.

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Once low-pressure venules are breached, intravasation of glycine, which is at a positive pressure, occurs. It is estimated that a dose of as little as 100ml may be fatal, owing to CNS toxicity. Hamou has reported one such death (1988). Significant systemic absorption of irrigating fluid with a rise in central venous pressure and fall in haematocrit due to haemodilution has also been reported with the Nd-YAG laser technique, and was considered to be excessive (Morrison et al 1989). Similar problems have been reported by Baumann et al (1990).

The cost of the apparatus required over and above that available in any standard operating theatre is much less than that of a Nd-YAG laser - approximately £4,000. However, a skilled hysteroscopist is still required, and there is a significant 'learning curve' effect, such that considerable experience is required before useful results are to be expected.

Hysteroresectoscopy is now becoming very popular in the UK, and there are several centres actively

engaged in assessing this technique at the time of writing.

There is now available a device which is capable of accurately measuring the volume of distension medium passing into and out of the uterine cavity, capable therefore of warning of large volume absorption. The machine is also capable of regulating intrauterine pressure vary accurately, to minimise intravasation. However, the situation may arise where an excess of medium has been absorbed, and the operation incomplete, when the only option is to abandon the procedure.

With time, the usefulness or otherwise of this technique will become apparent. Stirrat <u>et al</u> (1990), have pointed out the need for a controlled randomised trial against hysterectomy in order to accurately assess the long term effects.

1.6. Hyperthermia

1.6.1. Introduction

Several hundred years ago, the Greek physician Parmenedes recognised the potential beneficial effects of heat for a range of diseases, particularly malignancies. Hippocrates recognised the healing effects of fever, and felt that fever was a natural response of the body to infection. Since, those times, raising the temperature of tissues either of the whole body or locally, until recently, has been restricted to the treatment of malignant disease and occasionally genitourinary tract infection, since it was known at the turn of the century that gonnococcus is very heat sensitive.

Normal body temperature is in the range of 35.1 - 37.7 degrees celsius (Hahn, 1984). When body temperature approaches 42 degrees, the clinical picture of heat exhaustion occurs, followed by death if that temperature is exceeded for any length of time. Death occurs primarily because of massive skeletal myolysis with consequent renal failure; later CNS damage occurs

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especially to brain. There is a good biological basis
for the critical temperature.

At temperatures a few degrees above body temperature
the first change to occur at the cellular level is
denaturation of spectin and actin, protein components
of the cell wall and cytoskeleton. Human cells appear
to be capable of surviving such effects until
temperatures above 42 degrees are reached, when central
retraction of membrane, loss of microvilli, concentra-
tion of organelles in a juxtanuclear position, rounding
up of the cell and blebbing of the cell wall occur
(Coakley, 1987). Provided exposure time does not
exceed that outlined below for any given hyperthermic
temperature (in vitro), the cell is apparently able to
survive (Westra and Dewey, 1971, see figure 7).

Hyperthermia refers to the heating of tissue for the
purpose of destruction or inactivation of component
cells.   Usually this technique is used locally in the
treatment of malignant disease, although whole body
heating has been tried in the treatment of leukaemia.
Temperatures in the range of 44 - 53 degrees are
employed either alone or in conjunction with

radiotherapy (Streffer, 1977).

In vitro, mammalian cells survive for approximately one hour at 43 degrees and this thermotolerance time is approximately halved for each degree rise (Gerweck, 1977). At hyperthermic therapeutic temperatures, irreversible cell membrane, enzymatic and nuclear damage occur and the cell is rendered incapable of function (Hahn, 1984).

At one time it was conventional, therefore, to express hyperthermia doses in terms of 'equivalent minutes at 43 degrees'. However, it has become apparent that this relationship has little application clinically, since the in vivo situation is not directly related to that in vitro (vide infra). In fact, hyperthermia tends to be given in tolerance doses in the management of cancer, in much the same way radical radiotherapy is given, rather than using the principal outlined above. This is because clinically, much higher doses of hyperthermia are needed to achieve tumour toxicity than those predicted by in vitro models.

1.6.1.1. Experimental data

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Surviving
Fraction
(log)

10^{0}
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}

47° 46°   45°   44 5°   44°   43°

0   15   30   45   60   75   90   105

Minutes Of Heat Treatment
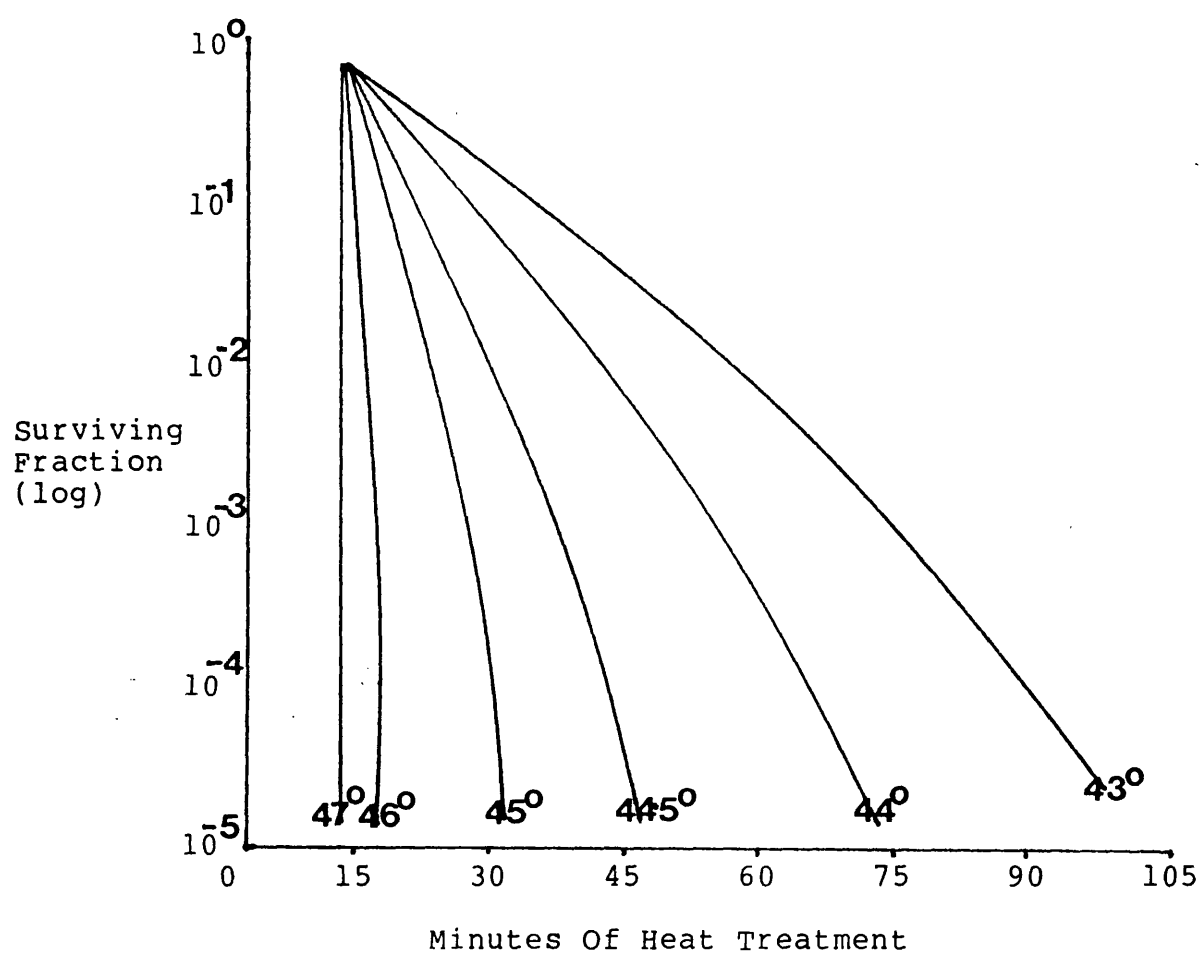
Figure 7 .. Hyperthermic Cell Survival Curves.

Chinese hampster cells were cultured in vitro, and exposed to various temperatures, controlled within +/- 0.1 degrees celsius (Westra and dewey 1971).

Cell survival was assayed by colony formation ability.

Hyperthermic cell survival times are based on either animal experiments, or more commonly tissue culture experiments. On general principles care must be exercised when extrapolating to the _in vivo_ situation, never more so than in the case of hyperthermia. Cells exposed to heat _in vivo_ are in a much more protected environment compared to those _in vitro_. Despite the fact that very accurate thermometry is possible during clinical hyperthermia, it is impossible to be certain that this is a true measure of the temperature of all the component cells _per se_.

Moreover, there are a number of specific reasons why experimental data may not explain the case _in vivo_.

Firstly, it has been demonstrated that there are changes in certain parameters of tissue culture media as a result of temperature change which may themselves affect cell survival: density, pH, viscosity, ionisation and gas solubility, including oxygen (Brock, 1978).

Secondly, most studies of cell death with hyperthermia look at simple cell proliferation or its absence as a

marker of cell damage (of interest in cancer therapy). The case with endometrial cells is not so clear-cut. There is no data available at the present time which would allow measurement of some marker of cell damage to those cells comprising the basalis layer and directly equate this with cell inactivation or death. However, in vitro histochemical studies do record the extent to which tissue has been heated (see experimental text) to relatively high temperatures (approximately 60 degrees intracellularly, required for G6PDH denaturation). However, such studies are likely to underestimate the degree of tissue destruction, since tissue damaged hyperthermically (ie, by exposure to lower temperatures for extended time periods) will not be elucidated (also see section 3).

Thirdly, although a certain fraction of cells survive the immediate effects of exposure to heat, there are late manifestations of previous exposure such as impaired capability to reproduce and synthesise certain proteins (Henle and Dethlefsen, 1978). Some cells have been shown to develop thermotolerance, and it may be that the late manifestations mentioned are part and parcel of this phenomenon.

For these reasons it is impossible to directly equate thermal dose with precise cellular/tissue effect, much less clinical effect. The situation is made even less clear by the fact that it is impossible even with sophisticated techniques to accurately assess tissue destruction after hyperthermia. Although electron microscopy is able to demonstrate some of the earliest intracellular changes associated with heat damage, no one has been able to devise a test that accurately assesses death/survival of cells (although, as previously mentioned histochemical studies go some way towards this).

Many workers have attempted to devise techniques which accurately differentiate between live and heat inactivated cells, besides looking at simple cell proliferation. These include cell morphology (Schrek, 1966), cell migration (Friedgood, 1928),whether cell colonies are formed or not (Pincus and Fischer, 1931), and trypan blue exclusion tests (Strom et al, 1977). All of these tests give results which are both incongruent with each other and with in vivo effects.

In the final analysis, the only meaningful test of hyperthermia effects are clinical. All else is, at best inaccurate, at worst misleading.

1.6.1.2. Other clinical applications

The only other application of hyperthermia to date other than the obsolete heating of the genitourinary tract for gonnorhoea treatment, is urological. Yerushalmi (1985) has reported the use of a transrectal microwave probe, driven at very high frequency (2050 MHz) to heat the prostate in benign hyperplasia/prostatic obstruction, in high operative risk patients. The results are 'promising', but the technique has yet to be fully assessed. French workers are producing an RF generator and transurethral probe for delivering lower frequency energy in order to capacitatively heat the prostate for the same condition.

1.6.2. Methods of Generating Hyperthermia

Tissue heating is achieved either by direct surface

heating (percutaneous hyperthermia), implantation of heating elements within the tissues (interstitial hyperthermia), or by high intensity ultrasound (Streffer 1977). These heating elements may either be driven by direct heating, such as irrigation with hot water, or by the passage of alternating currents between two electrodes, with the target tissue acting as the conducting medium between them. In clinical practice, the most commonly employed electromagnetic current is radiofrequency (Hand 1987).

1.6.3. Radiofrequency Electromagnetic Thermal Energy

One method of generating heat in tissue is the application of radiofrequency electromagnetic (RFEM) energy in the range of 500kHz - 2-3gHz (Hand 1987). We chose 27.12MHz because this is an assigned frequency for medical use, signal generators capable of producing such a signal are easily obtained, and the physical characteristics of thermogenic effects are ideal for application to the endometrium.

At this frequency an electric field is set up around the applicator, in this case the RF thermal probe, and

tissue lying within that field is subject to heating. Thus direct contact is not absolutely necessary for a therapeutic (histotoxic) effect. The power of the electric field falls off geometrically with distance from the RF thermal probe, in such a way that energy penetration beyond 7mm is minimal (Hand 1987). Thus RFEM is the ideal method of heating the endometrium in a precisely controllable fashion; by altering the amount of power delivered (which is easily measured) and the time it is delivered for, a very specific amount of tissue damage is to be expected.

In vivo, the probe, uterus, patient and external 'return' electrode form a resonant series circuit which is driven by the RF signal source (see figure 8). In vitro the same applies, but the 'rest of the patient' plays no part in the circuit. With the circuit set-up, the output of the RF generator is tuned to the capacitative and resistive components of the resonant circuit such that maximum power delivery is obtained, in much the same way that a radio set is tuned to a station to give the strongest sound. Tuning is monitored using a power meter which registers two parameters: incident power (the total amount of power
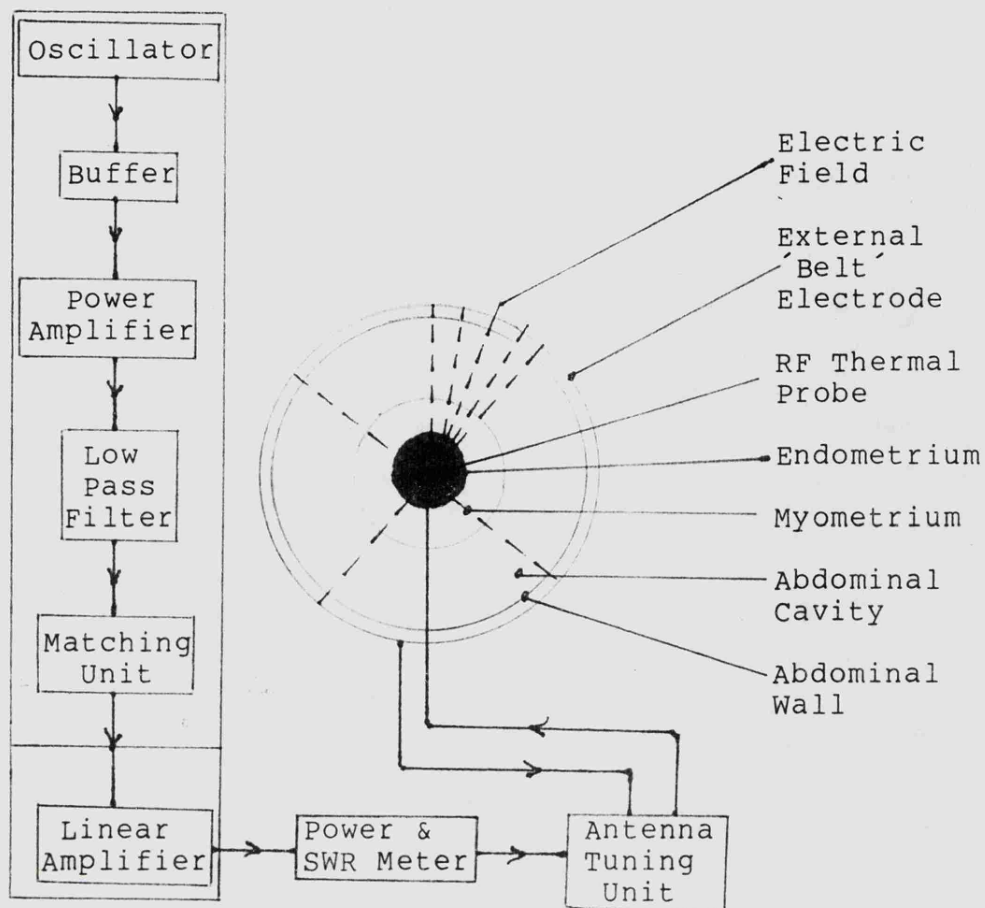
Figure8. Block Diagram Of Components Of RF Generating Apparatus And Patient Circuit

produced by the RF generating apparatus to which the
tissues are exposed), and the standing wave ratio
(SWR). The SWR is a numerical comparison of voltages
of the incident signal and the 'return' signal. At a
ratio of 1.0 the voltages are equal, and 'reflected
power' is zero, ie. all of the incident power is
absorbed by the tissues (as heat), due to the fact that
biological tissues behave as a lossy capacitor under
these circumstances.

1.6.4. Hyperthermia and endometrial ablation

Hyperthermic tissue destruction therefore uses a
completely different principle of tissue destruction
compared to laser or diathermy. Much lower tempera-
tures are employed, for much greater exposure times
(for any given area of tissue). The concept of 'total
simultaneous endometrial ablation' (TSEA) must be
introduced here. With laser or diathermy, endometrial
ablation is achieved by destroying small individual

areas, and are therefore time consuming. Although hyperthermic endometrial ablation using the RF thermal probe requires a number of minutes exposure time, a larger proportion of tissue is treated simultaneously.

The theoretical advantages of the RaFEA system over the other two commonly used are:

1. Safety. Much lower temperatures are used, and perforation of the uterine wall should be very rare, since the probe is 10mm in diameter and blunt ended. Moreover, the tuning circuit does detect when the probe is outside or partially outside the uterus. The risk of exposure of other pelvic structures to destructive energy is therefore less. No toxic distension media are required as is the case with the hystero-resectoscope.

2. Ease of use. Apart from placing the RF thermal probe and performing simple pre-treatment diagnostic hysteroscopy, no special skills in operative hysteroscopy are needed, as is the case with both the Nd-YAG laser probe and the hystero-resectoscope.

3. Speed. TSEA using the RF thermal probe should not take longer than 20 minutes, although experience with the technique is required to finalise this. Certainly, TSEA should be much quicker than Nd-YAG (approximately 60 minutes) or the hystero-resectoscope (40-60 minutes).

4. Cost. If the RaFEA system were produced commercially, a set of equipment would be considerably less than the prototype, which cost approximately £50,000. A set of hystero-resectoscope instruments with video etc. costs approximately £30,000. A Nd-YAG laser machine costs around £70,000.

However, safety is of paramount importance, and although the advantages of avoiding cutting tissue (and therefore of potentially incising blood vessels) and fluid risks are valuable, it must always be borne in mind that with RF ablation, the WHOLE patient must be paid attention to at all times in order to avoid complications occurring as a result of the patient being surrounded by an electric field, notably burns (see Section 2 - Safety).

1.6.5.   The radiofrequency thermal probe

From physical and engineering points of view, electromagnetic applicators are antennas which couple power into media (ie. target tissues). The biological effects of the energy delivered by the applicator are dependent upon the electrical properties of the tissues and the size, shape, operating frequency and position in relation to target tissue of the applicator itself (in this case the RF thermal probe).

The therapeutic action of this device relies upon its ability to deliver RFEM energy to the endometrium with which it is in close apposition. The design, development and structure of the device used in this study is described in detail in section 2, but is essentially a rod capable of accurate placement within the endometrial cavity.

Once the probe is placed into the endometrial cavity, good functional apposition between it and the endometrium is achieved for most of the surface area of the cavity owing to four factors. Firstly, despite the fact that the cavity widens superiorly and opens out at

the ostia, the natural elasticity of the tissue holds it against the probe much like a foot in a sock. Secondly, because the cavity lining is very wet, although it is irregular, good contact in terms of propogation of RFEM is achieved because biological fluid is a good conductor. Thirdly, as mentioned before, this device relies upon an electric field effect, so that physical contact is unnecessary for the heating effect. Finally, some 'longitudinal' conduction of heat presumably occurs from relatively warm to relatively cool areas as would be expected as the demands of thermodynamic entropy are satisfied. Later probe designs (not included in the experimental programme recorded in this document) have angulated rotating tips in order to maximally distribute the RF energy in larger cavities.

1.6.6. Unwanted Heating

Heating of non-target tissue, particularly bowel and bladder, is theoretically minimal (and this was confirmed experimentally) PROVIDED the thermal probe and thermal guard are sited correctly and maintained scrupulously by the surgeon in the correct position.

Three major factors prevent thermal destruction from affecting other pelvic/abdominal structures, and the outermost layers of the uterus:

1. They physical nature of the electric field generated by the RF apparatus, and applied to the geometry of the system used (ie. the external 'belt', patient and RF thermal probe), is such that the strength of the electric field and therefore heating effect, falls off as a geometric function of distance. Heating effect beyond approximately 7-10mm is not significant.

2. The target endometrium and basalis layer are thin compared to the thick walled uterus. The myometrium is a poor conductor of heat.

3. The massive blood supply of the uterus, maximal through the myometrium lends a powerful cooling effect to the body of the uterus.
(vide infra).

1.7. Experimental Rationale

1.7.1.   In Vitro Studies

The approach that was adopted in the investigation was first of all to test the ability of the RF thermal probe to produce a heating effect under in vitro conditions. Fresh hysterectomy specimens were exposed to RF energy, and examined in two ways. Firstly, temperatures were recorded at various depths within the uterine wall in order to demonstrate that it was possible to heat the endometrium without undue heating of the deeper layers of the myometrium or the serosal surface. In the absence of blood flow, this represented a 'worst case', since in vivo perfusing blood would tend to cool the outer uterus and hence lend a protective effect to other pelvic organs. Secondly, some marker of hyperthermic tissue damage was needed, but because there are no histological markers of damage at these relatively low temperatures, a histochemical technique was employed to 'record' tissue exposure to heat by testing samples for denaturation of a critical cellular enzyme. This technique has been used to study the effects of the laser on tissues

beyond the area of immediate destruction in vitro (Reid & Sharp 1988). This is not the case if the uterus is left in situ after RaFEA treatment in vivo followed by hysterectomy at a later time. This time interval would allow a pathological response to express itself, and therefore histological markers would become detectable.

It should be appreciated that there is no way of accurately assessing tissue damage immediately after exposure to hyperthermia. Histotoxic effects are due not only to direct, immediate thermal damage to critical cellular macromolecules, especially in the cell wall, but more subtle effects whose final consequence in terms of cell function are delayed (see Introduction, 'Hyperthermia').

It is therefore impossible to analyse tissue immediately after exposure and equate this to clinical effect in any accurate way, including looking at cellular enzyme denaturation. This was confirmed by examining hysterectomy specimens after in vivo exposure of the endometrial cavity to RF heating to hyperthermic temperatures. Heating tissue to temperatures below those required for enzyme denaturation, if those

temperatures are maintained for a sufficient length of time, will result in irreversible tissue necrosis despite intracellular enzymes remaining active.

The final and only meaningful test is that of clinical trial.

1.7.2. In Vivo Studies

Having demonstrated that it was possible to selectively heat the endometrium, and that despite the irregularity of the shape of the cavity the majority of the endometrium was exposed to RFEM thermal energy, it was felt justified to proceed to in vivo experiments.

Animal Studies

Animal studies were considered but rejected on the grounds that any results would have been difficult to extrapolate usefully to the clinical situation. Even with animal study results, the 'step' into human testing would still have to be made. Moreover, precise comprehensive monitoring of desired and possible undesired heating was performed (thermometry) allowing

any in vivo experimentation to be terminated at the first sign of non-target tissue heating.

All in vivo experiments were performed with the consent of patients after discussion on interview with the author.

RaFEA Testing During Hysterectomy

Histochemical examination of hysterectomy specimens was undertaken after RF endometrial ablation in volunteers just prior to hysterectomy in order to ensure that no excessive purely thermal destruction of tissue was occuring, especially at the cornua, isthmus and cervix.

In order to detect any unwanted thermal effects upon blood, samples were taken from an isolated uterine vein during RaFEA treatment at abdominal hysterectomy. There have been no such studies performed before as far as the author is aware, either for laser or electrosurgical endometrial ablation. No systemic haematological complications have been reported after these procedures, but during RaFEA therapy the whole of the endometrium is exposed simultaneously with a consequent larger thermal dose. The theoretical possibility of

significant deleterious heating effects on blood were therefore considered. Heating of whole blood accelerates coagulation (Coakley 1987), thus activation of a coagulation cascade was of concern.

The earliest indicator that blood has been exposed to heat is red cell morphology. Although red cells fragment at temperatures around 50 degrees Celsius, microscopically detectable changes do occur after exposure to temperatures above 46 degrees, variable with exposure times (Coakley 1987). Although blood flows through the uterus at approximately 1 l/min in the non-pregnant state, blood velocity will be considerably slower in the microvasculature, allowing prolonged exposure to thermal effects. In fact it proved very difficult to obtain blood samples during RaFEA treatment, and only small volumes were obtained. Insufficient blood was obtained to perform any meaningful analyses of coagulation. Microscopic examination of blood films prepared from samples failed to show any characteristic 'crennelation' of the red blood cells. Moreover, pre and post-operative coagulation profiles were normal and showed no change. No subject suffered any complication attributable to

haematological effects, either on red cells or coagulation.

Patient Numbers

In vitro and in vivo experiments, with the exception of the two pilot clinical trials, were aimed primarily at assessing feasibility and safety. Small numbers of specimens (in vitro) and patiens (in vivo) were therefore used. Moreover, thermometry results from individual patients were suprisingly consistent. Finally, there was considerable difficulty in obtaining patients who were suitable and willing to be involved in these complex experiments. For all these reasons, it was felt that it was not justified to repeat identical experiments in larger numbers of subjects.

Objective Analysis of RaFEA Effects

Hysterectomy some months after RaFEA therapy (when markers of the pathological response would be manifest) and histological examination would be the ideal method of objectively analysing tissue effects.

There are considerable ethical difficulties regarding a
second (possibly unnecessary) general anaesthetic,
however. Although two patients were very interested
initially in taking part in such a study, in the event
both were cured of their menorrhagia and declined
hysterectomy!

Several patients were hysteroscoped some months after
RaFEA treatment, and the endometrial cavity biopsied.
Others were subjected to Vabra aspiration as out-
patients. This provided objective (photographic)
evidence of RaFEA effects.

SECTION 2 - SAFETY

At the time of writing, it has become evident that the major concern about RF ablation is safety. Although over 250 patients have been treated by the author without further major complication, a multicentre trial has been embarked upon. At one of the centres involved, there have occurred three complications: an ECG pad burn, a pulse oximeter sensor burn and a vesicovaginal fistula. These have caused suspension of the trial, and a re-appraisal of the technique as a whole, especially whether or not it is too dangerous for routine use, and whether or not it should either be abandoned or confined to a specialist centre where full physics/engineering supervision is available, and used to treat those rare patients who cannot be treated by any other means (such as patients with very severe CVS disease who cannot tolerate intravasated fluids).

In each case of complication, the equipment involved and the procedure carried out were subjected to highly detailed inspection, and faults with both were identified. As a result of such analysis and problem identification, it has become clear that certain

features of the technique need to be thoroughly understood by everyone concerned with caring for patients undergoing the procedure. These are detailed below. Violations of safety protocol have also been identified in each case; the vital need for adequate education is discussed.

2.1. Introduction

The use of RF energy requires that special precautions are taken not only by the surgeon, but also the anaesthetist, theatre technicians and nursing staff, all of whom must be specially trained.

It is essential for safe practice that adequate precautions are rigorously followed at all times, and it must be appreciated by all concerned that RF energy must be treated with respect, and special rules apply, in much the same way as laser or diathermy use require their own particular handling protocols.

The most important feature of RF energy at the frequency employed for endometrial ablation, is that the patient is surrounded by an electric field during

treatment. In itself, this is harmless to both patients and staff provided adequate safety precautions are taken. RF energy will 'seek' a pathway to earth from the patient, although environmental levels of RF are well below those recommended by the Health and Safety Regulations (_vide infra_). The practical consequence of RF energy finding a point of earth contact is that current will begin to flow, and heating occur as a result. The current density and therefore heating effect will be maximal where impedence is highest, ie. at the patient/earth junction. This explains why any point earth contact results in skin heating and eventually burns if contact is maintained. A similar phenomenon occurs with diathermy use; such injuries are well recognised. Points of danger are where the patient may accidentally come into contact with metal table frames, stirrups and so on.

When laser was introduced into theatre practice it became necessary for all staff concerned to be made aware of the physical attributes of high energy light, particularly with regard to eyesight risk and the risk of burns. Some years previously, the then new technology of diathermy - actually relatively low

frequency RF energy, around 5-600kHz - was introduced into theatre practice, but is now widely used; appropriate safety rules are well known to staff.

Theatre safety in RF ablation requires that similar rules to those pertaining to diathermy are followed. The major difference is that during RF ablation, current flows continuously for some 15-20 minutes, rather than intermittently, as is the case with diathermy use. Any breach of regulations with the latter are therefore less likely to result in serious injury, since skin/tissue cooling is allowed to occur between energy applications.

2.2. Hazards at the operative site

It is essential that the surgeon is familiar with the physics of RF energy, the basic functions of the generating machine, and the underlying operative principles.

2.2.1. Bladder catheterisation

The bladder must be emptied prior to ablation, since a full bladder is much more likely to intrude upon the

operative field (ie. become 'trapped' by the vaginal thermal guard) and hence be at risk of heating and damage. There is also a theoretical risk that if the bladder is full of (highly conductive) urine, preferential heat deposition may occur anteriorly and place the bladder at risk.

2.2.2. Cervical dilatation

It is essential that the endometrial cavity be previously hysteroscoped to ensure that the cavity is within normal limits, ie. that there is no congenital abnormality or septum of any kind. Cervical dilatation must proceed smoothly and without any suggestion whatsoever of possible perforation or false passage creation. Unless the surgeon is completely confident that the endometrial cavity has been entered only, then the procedure should be abandoned. If there is excessive bleeding after dilatation (or before), ie. more than the small amount normally associated with cervical dilatation, then ablation must not be embarked upon under any circumstances. Excessive blood within the cavity causes inadequate heating of the endometrium, but more importantly may obscure the surgeons view positioning of the probe and/or guard.

2.2.3. Insertion of thermal guard

The guard must be inserted and rotated until the vaginal wall in all fornices, especially anteriorly, is fully retracted. The anterior wall and bladder must be fully swept back from the cervix at all times. The cervix must be captured centrally within the distal end of the guard, and maintained in that position at all times. The most efficient method of holding this geometry is by placing a stay suture through each of the anterior and posterior lips of the cervix, passing the suture material through the bore of the guard, and then fixing the sutures to the edges of the operators end of the guard. In this way, the cervix is held 'frozen' centrally, and it becomes impossible for the bladder to impinge on the operative field (ie. the retracted vaginal orifice).

2.2.4. Probe insertion

It is vital that the cavity dimensions are known, both from ultrasound (transcornual diameter), and length (from operative sounding). A probe should be selected

whose active tip heats the 'true' cavity only; it is
VITAL that the endocervical canal is not heated. The
myometrium at this point is thin and relatively poorly
supplied with blood. Damage is therefore likely to
occur easily, and the bladder is immediately
anteriorly. The probe should be inserted into the
cavity until the tip lies at the fundus, and must be
kept in this position at all times. It is essential
that the active tip is not permitted to 'wander' down
the canal such that endocervical heating occurs. This
is achieved by constant gentle pressure on the probe.
If there is any suspicion of perforation after
insertion, the procedure should be abandoned, or a
laparoscopy performed. Should perforation occur
unsuspected by the surgeon, the RF generator will
detect the fault because tuning of the system will not
occur within normal limits, since the probe will be
lying in a position 'electrically dissimilar' to that
encountered within the uterine cavity proper. This has
been confirmed since early work by measuring impedence
loading with the probe lying in both positions in
hysterectomy volunteers.

2.2.5. Ground plane electrode belt

The single most important factor is that the insulation of the belt must be intact. Currently used models are disposable, such that 'fatigue' of the plastic insulator is not possible. Breeching of this insulative layer may theoretically cause skin heating and possibly burns.

2.2.6. Maintenance of concentric geometry

It is vital that the concentric geometry of the cervix, probe and guard be maintained at all times. The patient end of the probe insulated shaft is captured centrally by the cervix, which itself must be captured centrally by the guard. The operator end of the probe insulated shaft is captured centrally within the guard by a 'spider' shaped clip which fits inside the guard.

2.3 - Hazards remote from the operative site

As previously mentioned, it is vital that 'diathermy rules' are followed, ie. that the patient must under no circumstances be allowed to come into contact with earthed metal. Danger points are the metal frame of

the operating tables, and the frames of the stirrups. The anaesthetist must be aware that if he touches the patients during treatment, a slight warming effect will be noted in the examining hand or finger. This is because current is flowing through him to the earthed floor. However, the resistance is so large to earth that current flow and therefore heating is minimal. It should not be interpreted by the anaesthetist as implying that the patients body temperature is any higher than normal (which it is not). Finger rings or previously placed metal-bearing surgical implants (eg. sterilisation clips) are not heated, since there is no earth pathway.

2.4. Patient monitoring

2.4.1. Electrocardiography

2.4.1.1. Safety

ECG electrodes offer a potential leakage of current from the patient to earth via the ECG monitor. It is therefore essential that a filter consisting of in-line high value resistors is interposed between the patient and the monitor in order to prevent skin burns

occurring under ECG pads. It is also essential that ECG pads are moist and of good quality, and that underlying skin is clean (viz. diathermy). The case of ECG pad burn resulted from faulty, dry, poorly conductive ECG pads incorrectly placed. Failure to observe these points may result in high impedence skin/pad joints and therefore burns. ECG pad burns due to diathermy are a recognised complication, and result from faulty skin/pad connection. As a further precaution, pads should be placed as far away from the operative site as possible, ie. on the outer aspect of the triceps muscle, and under the mid point of the left clavicle.

Monitors for use with RF ablation must always be checked for suitability before operation.

2.4.1.2. Quality of signal

A good quality trace may be obtained provided a monitor is used which conforms to government HSE Guidance Note PM 51, ie. able to withstand 3 V/m. Most modern equipment conforms to these standards. The field strength around the monitors during ablation reach a maximum of 2 V/m at full power.

2.4.2. Blood pressure monitoring

Since there is no conductive pathway between the patient and the automatic BP recorder (eg. 'Dinamap'), RF interference is not a problem. It is vital that BP is constantly monitored.

2.4.3. Pulse oximetry

2.4.3.1. Safety

The sensor head of the oximeter is completely insulated, but does contain metallic components. Heating and therefore burns of the finger may occur if there is any heating of the sensor head. This may occur in one of two ways: if there is a leak to earth such that capacitative coupling occurs between the finger and the earthed metallic components of the sensor head; or if there is heating of the metallic components themselves. The latter may occur if a current 'loop' develops due to induction within the sensor-connecting lines-monitor circuit. Earth leakage should not be possible under BS 5724, since the patient-connected side of the circuitry is isolated completely from earth. Current loop induction should

be prevented by maintaining the two lines to the sensor galvanically unconnected at both the sensor and monitor ends of the circuit. A patient has suffered a finger burn because the oximeter manufacturer joined the two lines together and to earth via a low value resistor to prevent diathermy interference. Unfortunately, this resistor failed to appear on the circuit diagram of the oximeter, and was therefore unanticipated. Later (safe) monitors use much higher value resistors, reducing current flow to negligible values.

2.4.3.2. Quality of readout

Only self-powered, RF resistant (ie. conforming to EEC standards) units are suitable. Avoidance of connection to mains earth is thereby achieved.

2.5. - Blood pressure maintenance

It is vital that the patients blood pressure is constantly monitored. Any significant falls in BP should lead to abandonment of the procedure. Uterine perfusion (along with other viscera) is preferentially reduced when BP falls. Drops in uterine perfusion may lead to excessive thermal penetration (vide infra).

2.6. - Equipment safety

British Standard 5724 (BS 5724) is a set of regulations and specifications laid down by government which prescribes certain standards of safety and reliability in medical equipment. In order to ensure conformity of the experimental apparatus to these standards, the patient had to be electrically isolated from mains earth, and additionally isolated from potential exposure to mains current leakage.

All mains driven components (the RF generator, and in most of the in vivo work the linear amplifier as well) were powered via a 1kVA mains isolation transformer. The advantages gained were:

1.   The patient was electrically 'floating', ie. not galvanically connected to mains earth, such that any exposure of the patient to mains potential would not mean that the current would flow to earth via the patient.

2.   Any high voltage 'spikes' in the mains supply would be damped out owing to the slow response of the transformer. Thus the supply to the RFG and linear

amplifier was 'smoothed', preventing exposure of the equipment to spurious high voltage.

3. If any fault occurred in the equipment such that the power supply became grounded (eg. a live shorting to chassis), then a fuse would not blow, and the equipment would continue to function.

4. The ATU uses air space capacitors, such that the output is completely isolated form the input in a galvanic sense. Thus the patient is isolated from mains current completely.

During thermometry, the Luxtron unit was also powered via the isolation transformer.

2.7. - Environmental safety

See Appendix 2. ERA test report number 5043/11D5/1 concludes that the maximal field strengths encountered in theatre at the time of treatment are well below the HSE guidance limit of 0.184 A/m (detailed mapping of field strengths is given in Appendix 2).

2.8. - Safety protocols

Continuously updated safety protocols are produced and distributed to all workers with the technique at all times. Guidelines are clearly laid out, and all staff involved are obliged to familiarise themselves with such protocols. Staff unfamiliar with the safety protocol are not admitted to theatre during ablation.

It cannot be emphasised enough that such protocols MUST be rigorously adhered to. Violations of safety protocol were identified as follows:

1. Vesicovaginal fistula:

a. The anaesthetist failed to inform the surgeon that the patients BP was low (as a result of a problem with the endotracheal tube); treatment was continued.

b. It was noted that a poor view of the cervix was maintained, and the anterior vaginal wall was not completely excluded. The fistula occurred in the anterior vaginal wall.

Both of these are in direct contravention of safety protocol.

2. ECG pad burn:

a. The skin was not cleaned, the pads were dry and

MULTI CENTRE CLINICAL TRIAL PROTOCOL

for

RADIOFREQUENCY ENDOMETRIAL ABLATION
(RaFEA)

24.08.1990

This Protocol supersedes all previous issues

This document MUST be read by all personnel concerned with RaFEA or entering the Operating Theatre during RaFEA

Presented by:

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Watford General Hospital
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Log: F:\WORDPRO\$$$$\ABLATOR\PROTOCOL 24.08.1990: N.J.Tyrrell

Figure 9. Obligatory reading for all theatre staff,

poorly conductive (from prolonged exposure outside their packaging).

b.   The ECG filter unit was not used, and the patient was connected directly to a mains powered ECG unit.

Both of these are in direct contravention of safety protocol.

3. Oximeter finger burn:

a.   The oximeter was left attached to the patient switched off (see 'pulse oximetry').

b. The unit was plugged into mains.

c.   The unit was not constructed to BS 5724 in that there was a significant earth leak via the (unmapped) low value resistor.

All of these are in direct contravention of safety protocol.

Familiarity, understanding and adherence to, safety protocol is absolutely vital.

2.9. - Education

The importance of staff education cannot be over-emphasised. Failure of staff to be aware of the

potential hazards of the clinical use of RF energy can

lead to serious complications, notably burns. It is

vital that not only the surgeon, but the anaesthetist

and theatre technician especially, are conversant with

the physical principles of RF use. Intensive training

must be given to anyone involved in the technique, who

must be satisfied that they have understood the

information imparted to them.

SECTION 3 - EQUIPMENT DESIGN & DEVELOPMENT

3.1 Design of the RF Thermal Treatment Probe

Object: The purpose of this exercise was:

To design and build a prototype of an instrument suitable for the accurate and safe delivery of RF energy to the endometrium.

The physical requirements of the RF thermal probe (RFTP) are that it is of a diameter and length which allows easy placement within the uterine cavity, and is safe and easy to handle for both patient and operator. The active tip of the probe must be of a length which precludes heating of the cervical canal, in view of the thin myometrium and proximity of the bladder. It was decided that the RFTP should be placed into the endometrial cavity under direct vision, so that a channel for a standard hysteroscope was required. However, later in the experimental series, we concluded that visualisation was both difficult and unnecessary-

and hysteroscopic insertion was abandoned.

Since only uteri which were clinically and ultrasoni-
cally normally shaped were to be treated, the length of
the 'active' end was fixed at 6cm, the usual length of
the uterine cavity. The length of the probe was fixed
at 30cm, since this allowed a standard hysteroscope to
fully engage the central channel, and just protrude
from the end to give a good view.

10mm was chosen as the RFTP diameter, since at this
size the active end would be of sufficient volume to
create an evenly distributed electric field density
without 'sharp corners', thereby avoiding areas of high
density and 'hot spots'. Moreover, a 10mm shaft is of
adequate size to give good apposition to the uterine
walls, facilitating central placement of the RFTP, but
also allowing relative ease of insertion.

Stainless steel was selected for the active end and
nylon for the rest of the shaft because of its good
insulative electrical properties.

At the operator end is a 5cm diameter nylon handle 10cm
long which allows a convenient grip, and also reduces

the proximity of the surgeon's hand to the signal input, which otherwise acts as a capacitative drain on the signal.

A stainless steel 1mm wire is set into the side wall of the central 4mm diameter channel which conducts the RF signal to the active end. This wire had to be kept as close to the centre of the RFTP as possible to minimise the capacitative drain on the RF signal due to the proximity of the patient's tissues, ie. the vagina (see figure 10).

The stainless steel and nylon components are all assembled with an interference fit, thereby avoiding bonding agents which are susceptible to degredation by sterilising agents.

Power enters the device via a 6mm diameter co-axial screened cable at the operator end, and is connected to the central stainless steel conducting wire. All of the materials used are sterilisable by a 15 minute submersion in a cold biocidal solution ('Toticide'). (See Figure 11).

Active tip

Insulated shaft

Handle

Input
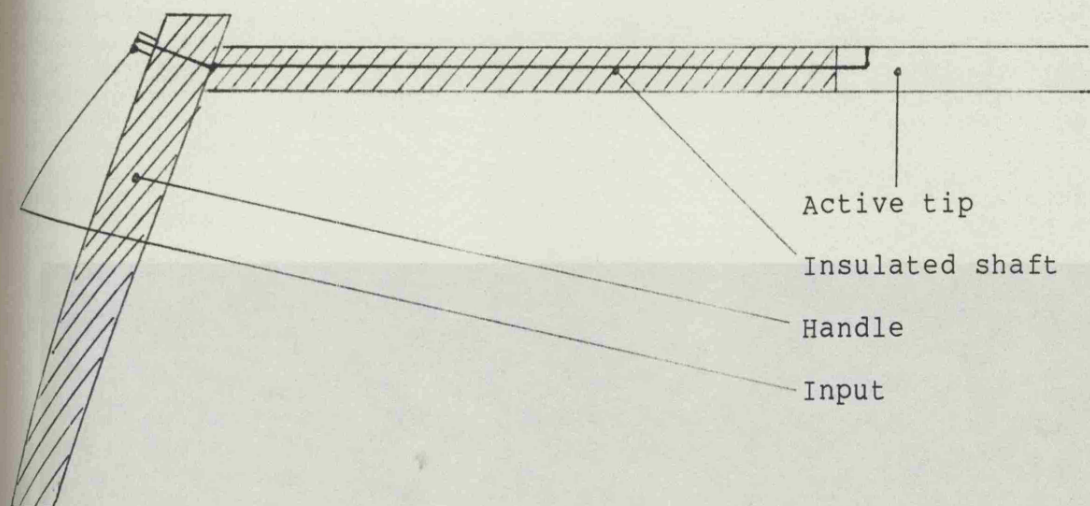
Figure **10.** The Radiofrequency Thermal Probe (x0.5)

Hysteroscope
Channel

Nylon
Casing

Conductive
Core
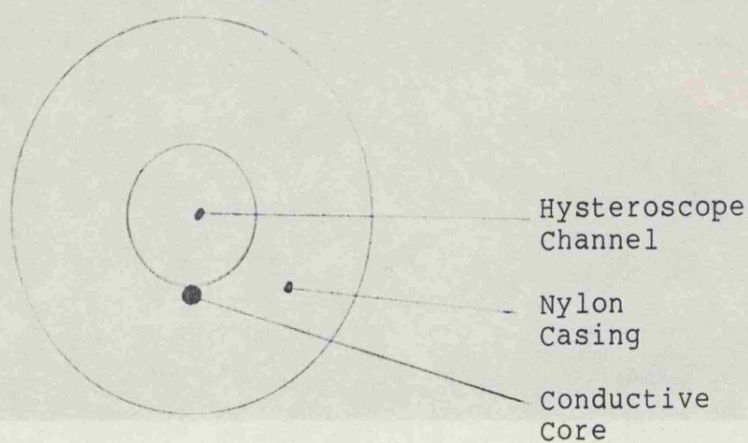
Cross section Of Insulated Shaft (x5)

Figure 11 . The prototype radiofrequency thermal probe.

3.2   Design of the External Electrode for Clinical   Use ('Belt')

Object: The purpose of this exercise was:

To design and construct a device capable of acting as a suitable external electrode for the 'return' side of the RF tuned resonant circuit that was safe, simple and easy to use.

The external electrode in the circuit does not have to be in direct electrical (in the sense of low resistance) contact with the patient.   Because the circuit formed by the RFTP and patient is relatively low resistance and low capacitance, a capacitative external electrode is appropriate in order to provide a more suitable impedence load for the RF generator, which requires a load of 50 ohms.

An ideal device would be a wide flexible band of metal, completely insulated.   This is not commercially available at the present time, although a purpose built unit may become available if commercial viability of

the RaFEA system becomes possible.

From existing materials, we selected a 10cm wide multiple channel flat computer interface cable, which is available in any length. A two meter length was used, and all the component conductive cores shortened together by soldering the leads, at both ends. One end was then encapsulated in non-conductive epoxy resin, and the other connected to a purpose multipin socket.

Thus a completely electrically insulated belt was formed containing 50 cores of wire, all forming a single electrode. A co-axial lead fitted with the matching multipin plug was used to connect the electrode to the return side of the RF generating apparatus (see Figures 12 & 13).

The 'belt' thus formed is waterproof, and is sterilisable in cold biocidal solution ('Toticide') for 10 minutes. Sterilisation was only required for the series of experiments involving RFTP treatment intraoperatively during hysterectomy, but not for routine use in the Phase 1 clinical trials.

Multicore
Computer
Interface
Cable

Insulated
Connector

Multipin
Socket
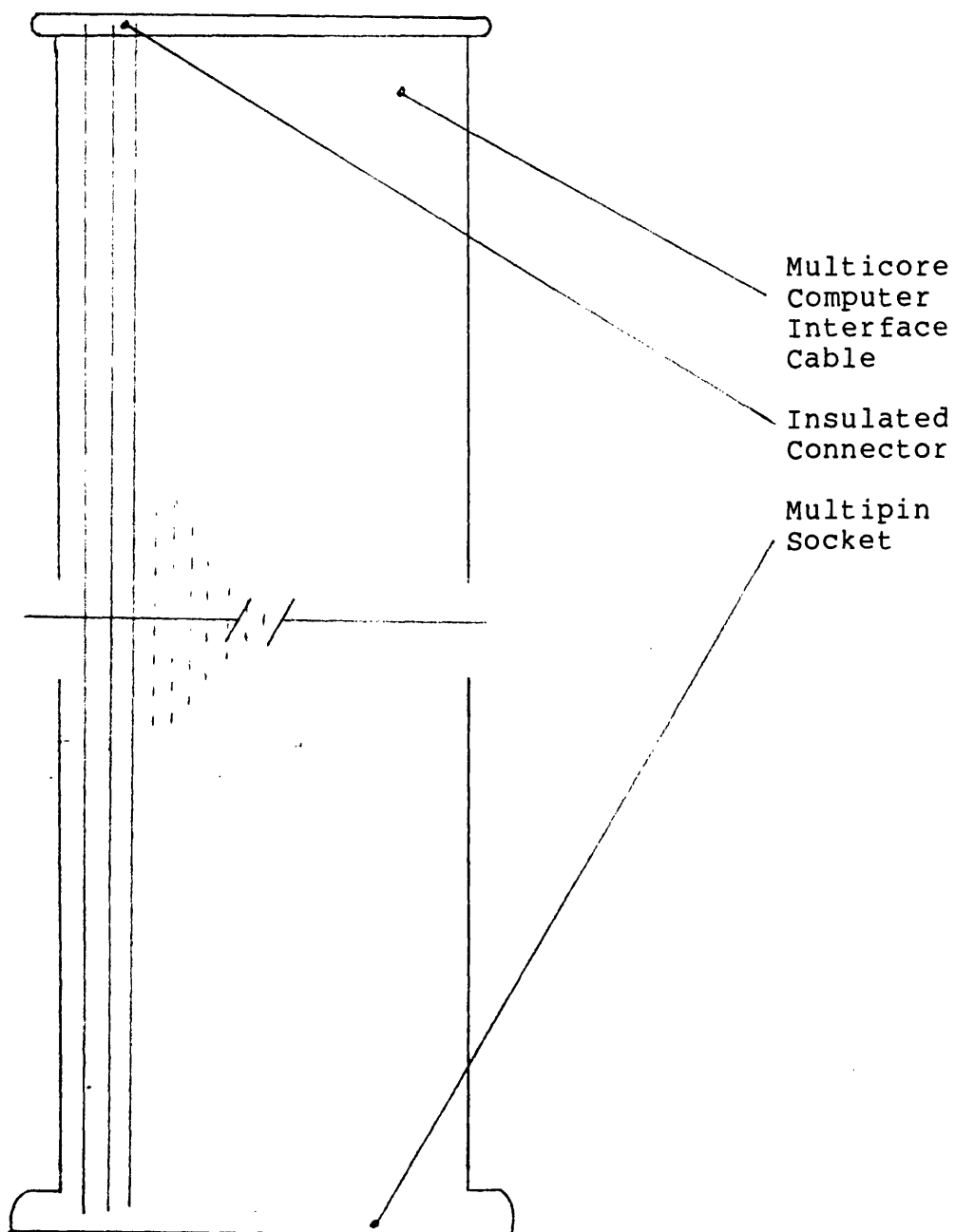
Figure 12   The External 'Belt' Electrode
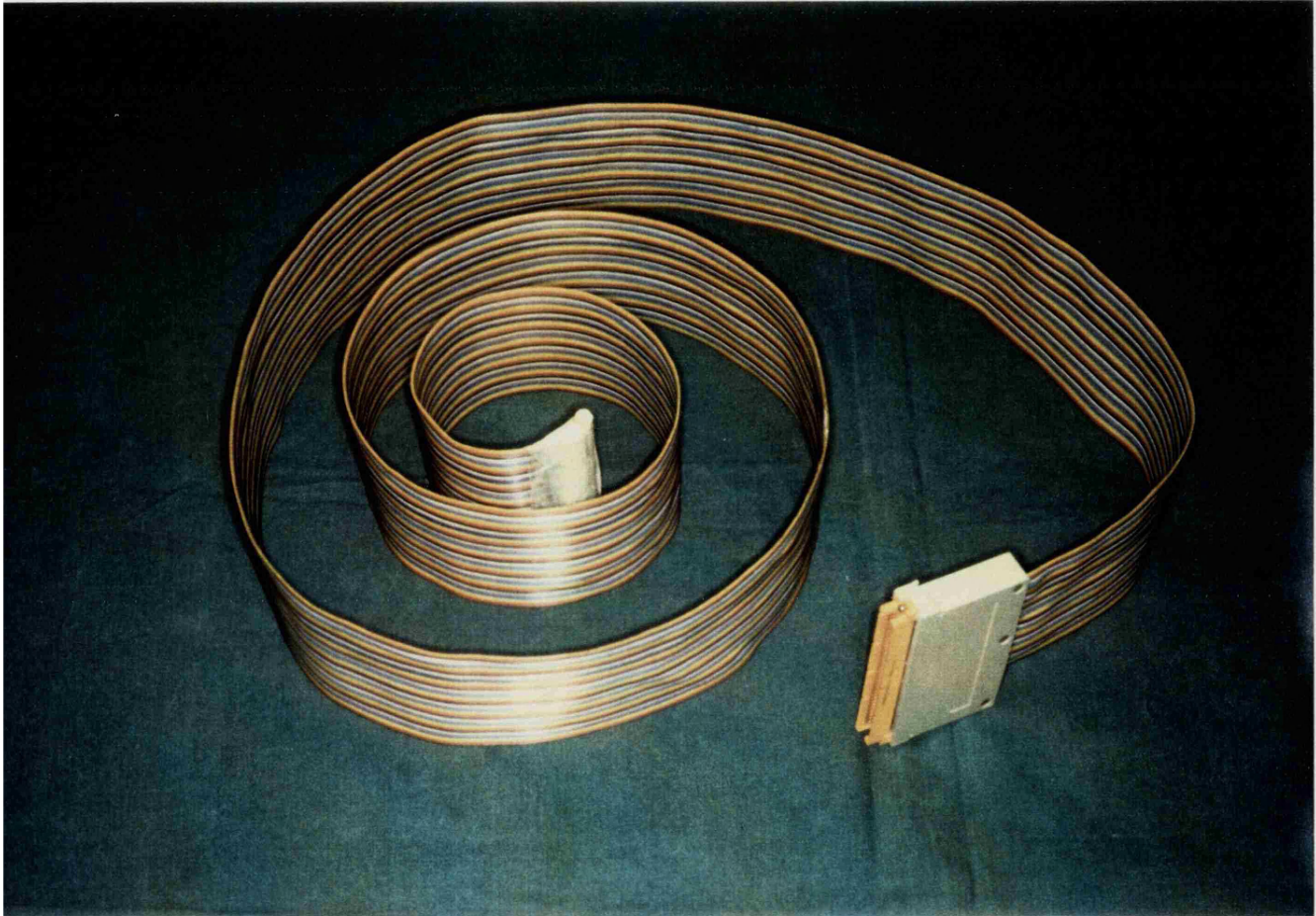
Figure **13** . The prototype insulated ground-plane

electrode ('belt')

The belt was fitted to the patient prior to general anaesthetic, by wrapping it around the waist, such that the inferior edge was at the level of the anterior superior iliac spines. Exact anatomical placement was not found to be critical, but this position allowed easy fitting with good apposition to the patient's skin. Loose fitting was avoided because this would weaken the therapeutic electric field, and there was also the theoretical risk of creating RF 'hot spots', ie. areas of high field density, on the surface of the patient, and therefore a heating effect. Firm, flat application excludes this theoretical possibility.

3.3. The RF Generating/Tuning Apparatus

The equipment used in all of the experimental work in this thesis was kindly loaned by the MRC Hyperthermia Unit, Royal Postgraduate Medical School, Hammersmith Hospital, courtesy of Dr Stan Field, Unit Director.

The signal source was a 'Kenwood' Transceiver Unit, set to a transmitting frequency of 27.12MHz. The output of this was coupled directly via a power/SWR meter to a 'Hea thkit' SA-2040 antenna tuning unit (ATU).

When it became necessary to boost the power output beyond 80 W incident, a matching 'Kenwood' 1 kW linear amplifier was added (see Figure 14).

These components are 'ready built' items, more usually employed for radio-communications. Thus the set of equipment was not purpose built, and certain precautions and modifications were necessary in order to guarantee patient and operator/theatre staff safety.

Reliability

The linear amplifier was the component most 'stressed' in that it was required to deliver a high power signal (550 W) for 20 minutes continuously. Under normal communications use, this high power would only be required for short periods during transmission. Between transmission, cooling would normally be permitted.

In fact, the equipment proved remarkably reliable, although a fault did occur in the linear amplifier on one occasion (a burnt-out relay).
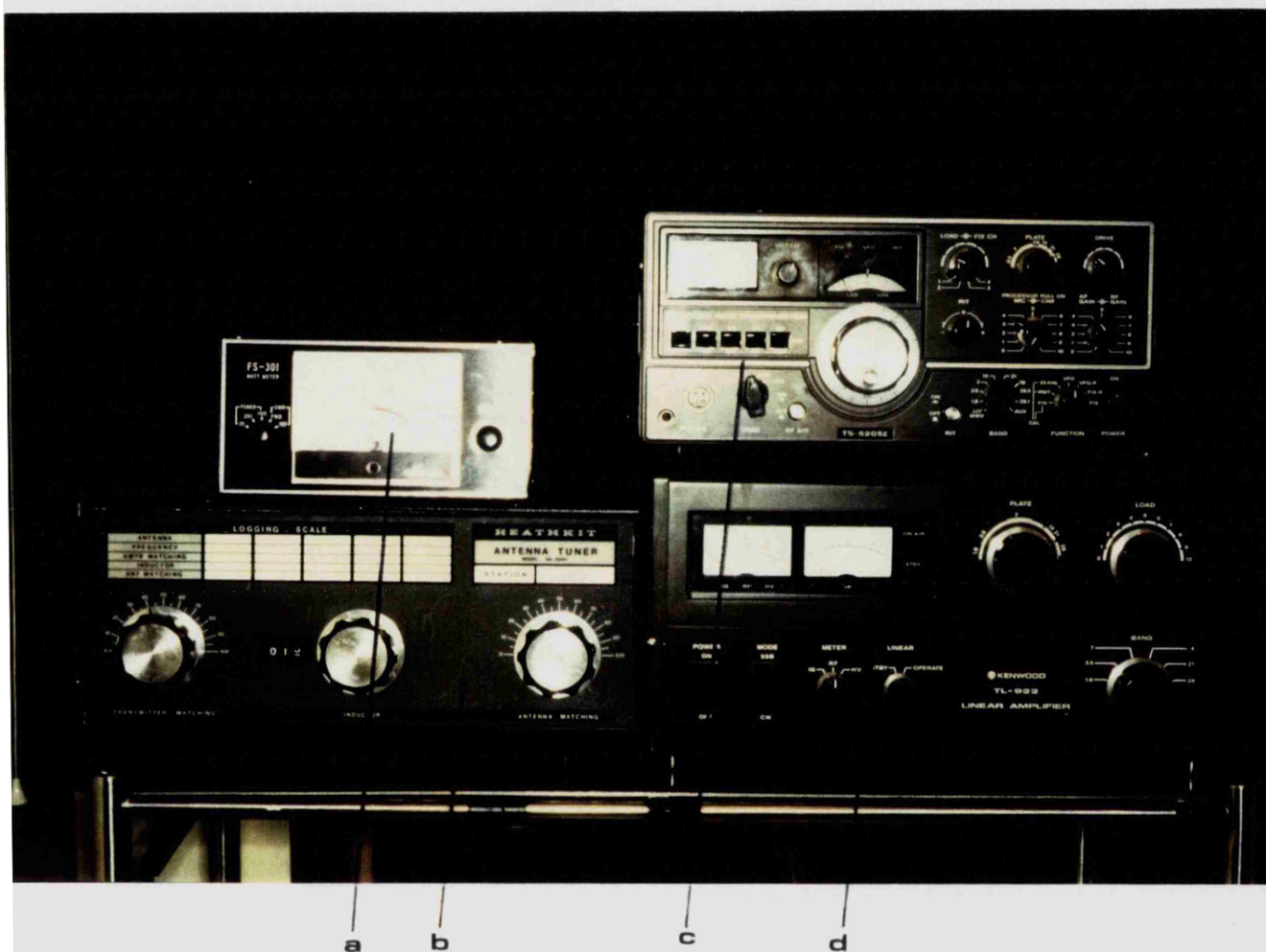
Figure **14** . The prototype radiofrequency generating

apparatus.

A - SWR/power meter   B - Antenna tuning unit

C - Transmitter unit D - Linear amplifier

3.4. Design of the Vaginal Thermal Guard/Speculum

Since no metal accessories may be used with the RFTP apparatus, at the beginning of the project, perspex cuscoes speculae were used (which are freely available commercially). In patients with a capacious vagina, it became apparent that a larger device was needed to maintain the vaginal walls (especially laterally) clear of the cervix, both to keep an uncluttered view and to prevent heating of the vagina (see Figure 15).

In two especially obese patients, the vaginal wall accidentally came into contact with the shaft of the prototype RF thermal probe, which had developed a fracture in the insulation. The anterior wall of the vagina was damaged, and vesico-vaginal fistulae resulted.

In response to these problems, a nylon version of an obsolete vaginal speculum (the Ferguson speculum, Rocket of London Museum), was designed and built. This consists of a dense, pure nylon tube, 50mm in diameter, 100mm long, which is slightly tapered at the distal

Figure **15** .   The radiofrequency thermal probe in situ

end, and cut at an angle to form the frustum of a cone (see Figure 16). The outer surface is ridged, with a reverse rake in profile such that the tube is easy to insert, but less so to remove. This prevents 'spontaneous expulsion' by the musculature of the vagina, which we initially found to be a problem.

Nylon is highly insulative, and is thus a good 'barrier' to capacitative coupling between the vagina and any low level 'radiation' from the shaft of the RFTP. Moreover, the vaginal walls are symmetrically retracted allowing a perfect view of the cervix and in situ RF thermal probe.

However, the surgeon MUST be perfectly certain that the probe is fully engaged at all times, and that the vagina and therefore bladder are fully retracted and central at all times. Moreover, the probe must be captured centrally by the cervix, which itself is lying centrally within the guard (see Figure 17). Failure to maintain a concentric geometry results in uneven heating and the possibility of injury to non-target tissues arises.

(See Section 2 - Safety).

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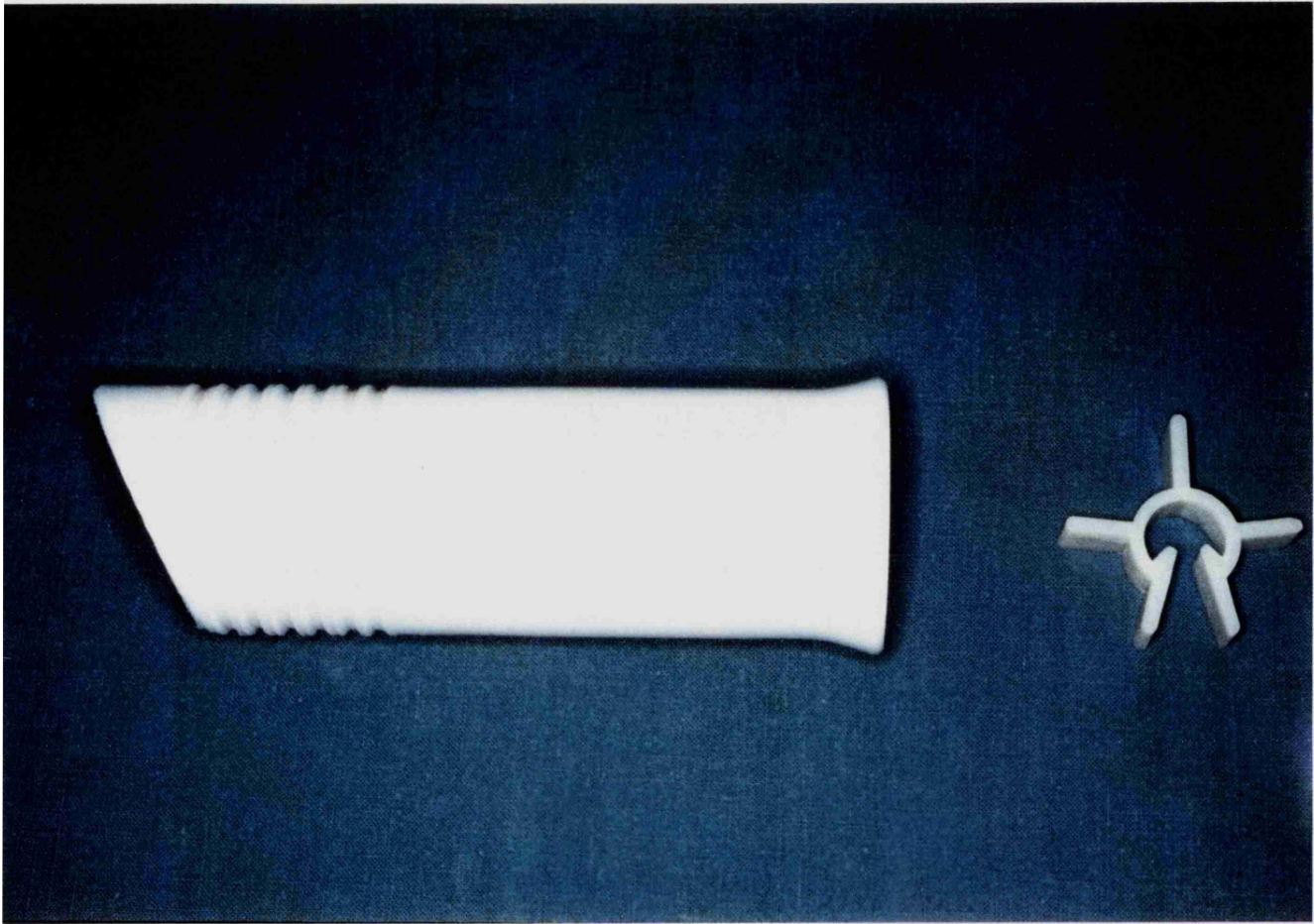
Figure**16** . The Thermal Vaginal Guard And Locating

'Spider' Clip.
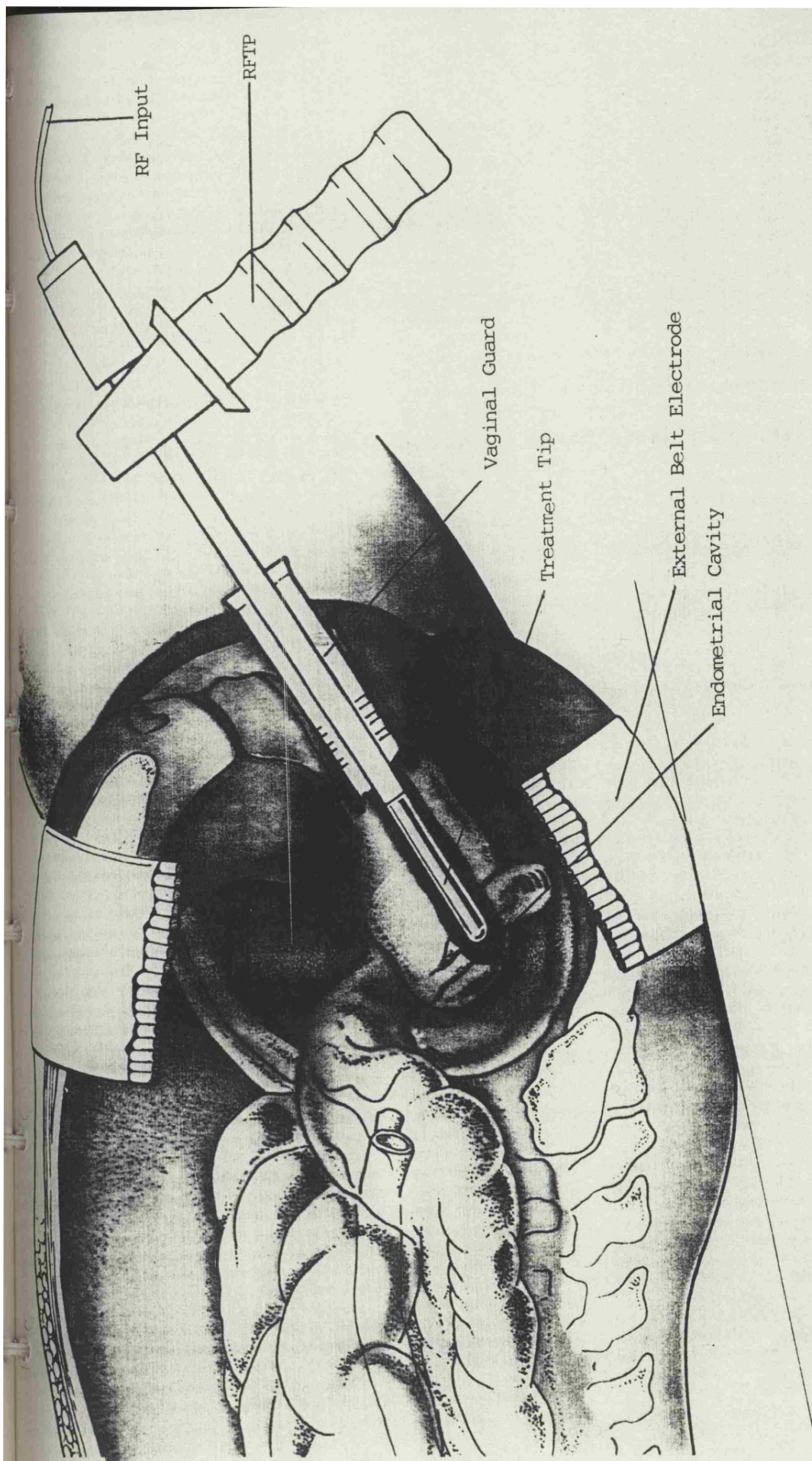
Figure 17. Schematic Diagram Of RFTP and Vaginal Guard In Situ, Saggital Plane View.

SECTION 4 - IN VITRO STUDIES

Object:

The purpose of this set of in vitro experiments was to:

1. Tune the RF resonant circuit comprising the RF generator, the RF thermal probe, fresh operative specimen uteri and an external electrode.

2. To characterise the thermal conductivity of uterine tissue.

3. To determine the extent of tissue damage resulting from RF thermal probe treatment under _in vitro_ conditions at temperatures compatible with cell death of target tissue (ie. the endometrium including the basalis layer).

4. To define the surface area of effective treatment within the uterine cavity.

Exposure of the endometrium to RFEM Energy

Patients, materials & methods

Criteria for patient entry were:

1. Age between 35 and 55 years.

2. A diagnostic curettage performed within six months showed benign endometrial curettings OR the indication for hysterectomy was simple uterovaginal prolapse.

3. There was nothing in the history suggestive of possible organic gynaecological pathology other than uterovaginal prolapse.

4. Consent was obtained from the gynaecological and pathology consultant to use the hysterectomy specimen for experimental work prior to routine histological analysis.

Seven patients were admitted, but two subsequently

rejected because of technical faults with the RFEM generating apparatus.

After abdominal or vaginal hysterectomy, the fresh specimen was transported to the physics laboratory immediately with a maximum delay of 15 minutes between excision and experimentation.

On the bench, the cervix was dilated to size 10 Hegar (10mm) in all cases, and the RF thermal probe placed fully within the uterine cavity.

Size 22 gauge intravenous plastic cannulae were then pushed through the uterine wall at 90 degrees to the plane of the cavity until the tip of the trochar needle touched the RF thermal probe within. The tip of the plastic cannula was then at 0mm from the probe. One cannula was left at this level within the uterus, and the remaining three withdrawn by measured amounts such that the tips were 5mm, 10mm and 20mm from the probe surface. The trochar needles were then withdrawn and thermometric probes introduced into the cannulae connected to a 'Luxtron' multichannel electronic

thermometer (see Appendix 1).

Excess fluid was mopped from the surface of the specimen, which was then sheathed with a plastic sheet, ensuring that the RF thermal probe and the temperature probes were carefully maintained in place.

The plastic wrapped specimen was then surrounded with a flexible aluminium diathermy pad for its entire external surface area to form an insulated (from the uterus) capacitance 'return' electrode.

The output from a 27.12 MHz RF signal generator was connected to the RF thermal probe via an antenna tuning unit (ATU) capable of varying the impedence of the electrical load presented by the thermal probe, uterus and return electrode which thus formed a resonant series circuit. Tuning was monitored using a power meter to monitor total power delivered and amount of power 'reflected', ie. not absorbed by tissue in the form of heat.

Baseline temperatures were recorded at 0mm, 5mm, 10mm and 20mm (ie. nearest the serosal surface) from the thermal probe surface.

With the RF generator set to deliver a very small amplitude signal (approximately 3 W), the circuit was tuned to maximise the amount of power deposited into tissue. In order to achieve this, the standing wave ratio (SWR) was monitored and maintained close to 1.0. Alteration of the capacitance, inductance and resistance characteristics of the ATU allowed circuit tuning. There was no rise in temperature with an incident power of 3 W.

Time was then marked using a stopwatch, the RF generator output rapidly increased to give 70 W incident power, with a SWR of 1.0.
Temperatures were recorded manually at ten second intervals (the update time of the Luxtron unit).

When the temperature at 5mm from the thermal probe surface had reached 70 degrees centigrade, the signal was switched off, and the Luxtron temperature probes

and the thermal probe removed. The plastic cannulae were left _in situ_. The external electrode and plastic sheath were removed, and the specimen immediately sliced transversely at the level of the isthmus, mid-body and at the level of the tubes using a large scalpel. Tissue slices approximately 3 mm thick were taken at these levels, and wedge-shaped sections cut to include all layers of the uterine wall identified by means of a coded label and plunged into liquid nitrogen. A single midline slice of tissue was also taken at the fundus in the saggital plane and similarly stored.

All tissue samples were saved for histochemical analysis (see Appendix 3).

The remainder of the specimen was sent for routine histological examination.

This procedure was repeated in four other specimens.

Patient Details:

Patient Init's	Age	Uterus Dimen. (mm)	Cavity Length (mm)	Previous Histol'y	Endom. Depth (mm)	Day Of Cycle
1. RM	41	100x63	77	Benign	4.2	11
2. BL	34	85x60	76	Benign	5.1	16
3. PC	49	110x70	84	Benign	6.3	18
4. SS	44	90x55	78	Benign	6.9	18
5. RS	50	95x60	80	Benign	7.0	22

Results

Using an RF signal at 27.12 MHz and altering the impedence load of the RF thermal probe/uterus/external electrode circuit, it was possible in all cases to tune the circuit to deliver 70 W power with a SWR of between 1.0 and 1.2 (ie. with minimal reflected power, indicating efficient deposition of energy into tissue).

Thermometric results are shown in Figure 18 as degrees

centigrade rise above baseline temperature plotted against time. The baseline temperature varied by a few degrees according to ambient conditions and exact time from excision to experimentation (range 28.3 to 31.0 degrees, and 11 to 15 minutes respectively). The data presented in Figure 18 represents temperatures which are average for the five specimens, but the results for each specimen were surprisingly similar (maximum variation 0.6 degrees centigrade).

Macroscopic examination of cut edges of treated tissue revealed a faint whiteness of the tissue adjacent to the thermal probe, but this was very difficult to see, and was impossible to photograph because the changed appearance was so subtle. Routine histological examination of the specimen failed to show any specific change that could be attributed to the RF heating (see photographs in section 6). An experienced consultant pathologist was unable to delineate heated from non-heated tissue in any case, as would be expected. Maximum depth of endometrium is shown above.
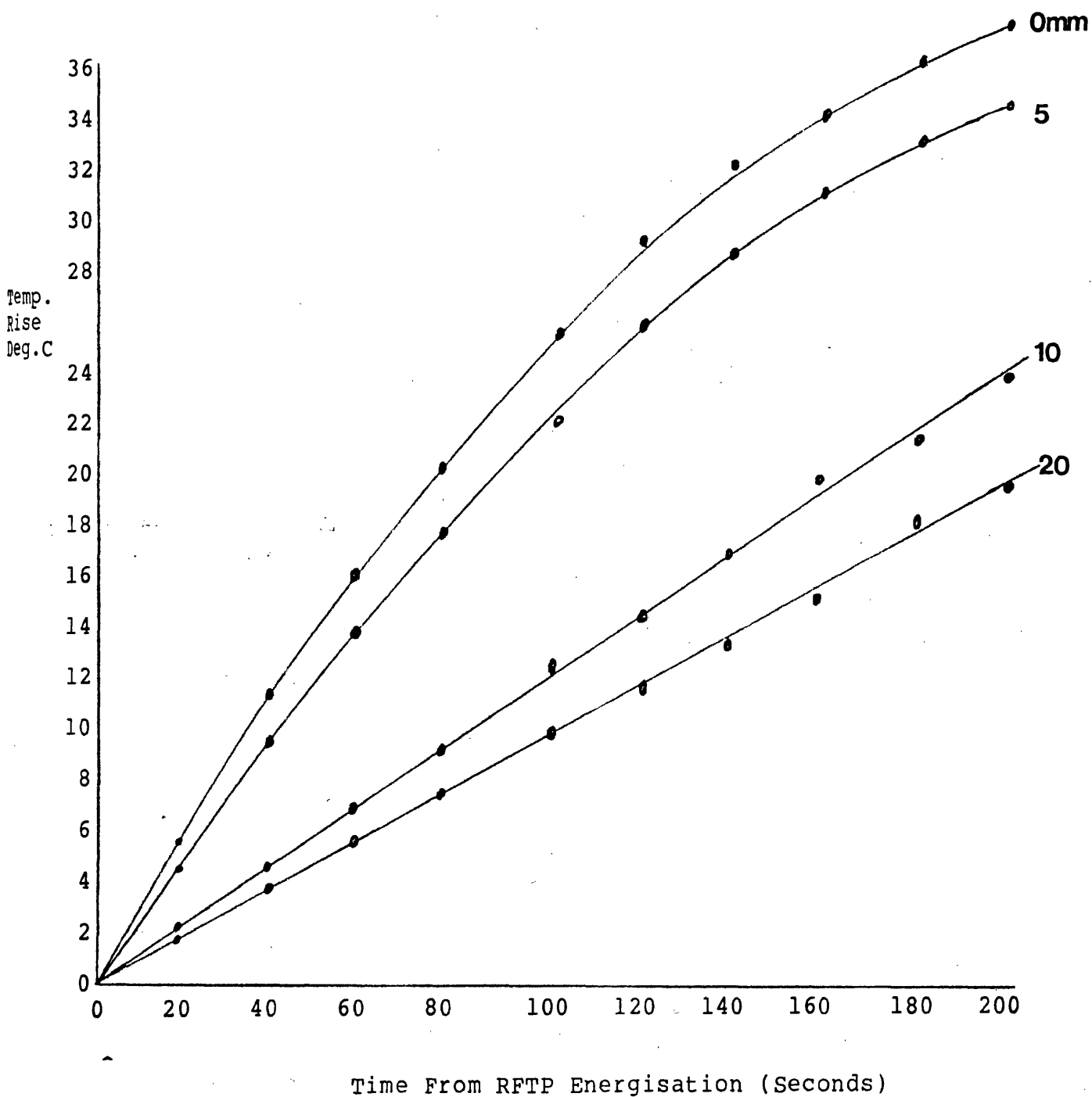
Graph **18**: Temperature Rise At Various Distances From
The RFTP During Treatment In Vitro.

(n = 5), points plotted are average values - maximum

variation of readings 0.6 degrees

The histochemical analyses showed that virtually all of the endometrial cavity had been heated to a depth of 5-8 mm, sufficient to cause denaturation of glucose-6-dehydrogenase (G6PDH). Tissue slices from the level of the isthmus, mid body, tubal ostia and saggital fundal slices showed a clear demarcation between heated and unaffected tissue. Vernier callipers were used to measure the depth of tissue destruction, and the results are overleaf.

Results of Histochemical Analysis of RF Heat Treated Hysterectomy Specimens:

Site Of Sample	Specimen Number				
	1	2	3	4	5
Isthmus	5.3	5.1	5.0	5.4	5.6
Mid body	6.2	5.9	6.3	6.6	6.2
Ostia (coronal)	3.5	4.1	4.3	3.6	3.2
Ostia (saggit.)	4.5	5.6	5.9	6.2	5.5
Fundal (saggit.)	6.2	6.6	5.9	5.8	5.1

Depth Of G6PDH Denaturation (mm)

Total Thickness Of Specimen (Endo- + Myometrium):

Site Of Sample	Specimen Number				
	1	2	3	4	5
Isthmus	14.3	12.9	13.8	21.0	15.8
Mid body	24.6	27.1	21.7	24.7	25.0
Ostia (coronal)	10.3	9.9	11.9	9.7	9.3
Ostia (saggit.)	10.1	9.4	9.1	9.8	8.9
Fundal (saggit.)	15.0	18.0	21.0	18.0	21.8

* These measurements do not take account of tissue shrinkage which occurs during tissue processing (approximately 15-20%), but since the myometrium and endometrium presumably shrink in equal proportion, percentage depth of tissue destruction remains a valid parameter.

Conclusions

1. Using the 'Kenwood' RF generator as a 27.12 MHz signal source and 'Heathkit' SA-2040 antenna tuning unit it is possible to drive the series resonant circuit formed by the RF thermal probe, uterus and external electrode such that a relatively high fraction of the output of the RF generator is absorbed by the uterine tissue in the form of heat.

2. It is possible to heat the endometrium in the __in vitro__ situation to sufficiently high temperatures for sufficient time compatible with a histotoxic effect, but the outer areas of the uterus remain sufficiently

cool that more extensive thermal damage does not occur.

3. Despite the uneven shape of the uterine cavity, RFEM energy delivered via the RF thermal probe is capable of heating the great majority of the endometrium to a relatively uniform depth.

Discussion

In the 'worst case' situation, where blood flow was absent, it may be seen that uterine tissue is a poor conductor of heat. When the endometrial surface temperature was 30 degrees above ambient temperature, the temperature at the uterine serosa was only 12 degrees above.

With meticulous thermometry, it was felt justified to proceed to the in vivo situation.

SECTION 5 - IN VIVO THERMOMETRY STUDIES

5.1 - <u>In Vivo</u> exposure of endometrium to RF heating at 70 W power

Object:

The purpose of this set of <u>in vivo</u> experiments was to:

1. Test the performance of the RF thermal probe in heating the endometrium <u>in vivo</u>.

2. To perform thermometry in extrauterine tissues during RaFEA in order to monitor exposure of other pelvic organs to thermal energy.

3. To obtain uterine effluent blood during RaFEA for red cell morphology, in order to monitor any haematological damage.

Patients

Criteria for entry:

Patients were admitted to the experimental protocol if:

1. They gave fully informed consent.

2. They were booked for an abdominal hysterectomy for intractable DUB.

3. A histological analysis of uterine curettings had excluded organic disease within the previous nine months.

Patients were excluded if:

1. They failed to give informed consent.

2. There was any history of serious intercurrent medical conditions.

3. They were excessively obese (greater than 90th centile weight for height). The reason for this was that intraoperative access to pelvic organs is difficult in obesity; much more so when there are a number of thermometry probes and blood sampling lines in situ.

Materials and Methods

Patients were judged preoperatively by a consultant anaesthetist who judged them fit and well (ASA 1). An ECG and chest X-ray were performed, and blood taken for cross-match, urea and electrolytes, liver function tests, coagulation screen (prothrombin time (PT), partial thromboplastin time (PTT), thrombin time (TT)

and fibrinogen levels ([Fib])), follicle stimulating hormone (FSH) and free haemoglobin. These tests were repeated six weeks after operation. Normality of the tests preoperatively was a condition for entry to the trial.

All patients gave informed consent after interview with the author. Ethical committee approval was obtained.

Two patients were selected for the first phase of the study:

Patient Init's	Age	Height (cm)	Weight (kg)	D&C Histology	Day Of Cycle
JM	38	161	61.6	Benign	12
MR	41	157	57.8	Benign	9

Blood Results:		
Parameter	Patient JM	Patient MR
U&E *	Normal	Normal
LFT **	Normal	Normal
PT	13 sec	15 sec (12-15 sec)
PTT	27 sec	32 sec (25-40 sec)
TT	10 sec	10 sec (10-13 sec)
[Fib]	3.1g/1	4.0g/1 (2-4.8g/1)

Free Hb	0	0
FSH	12 IU/ml	9 IU/ml

(Premenopausal FSH = <30 IU/ml)

* U&E includes serum urea, creatinine, sodium and potassium

** LFT = liver function tests includes serum total and conjugated bilirubin, alkaline phosphatase, alanine transferase, aspartate transferase and gamma glutamyl transferase.

Chest X-Ray, ECG and blood pressure were within normal limits.

The patient was prepared for theatre, and a general anaesthetic given by a consultant anaesthetist. She was placed in the modified lithotomy position (legs and hips partially flexed) in order to provide access to both vagina and abdomen.

The vagina was cleaned with an aqueous antiseptic agent and the cervix dilated to size 4 Hegar. A diagnostic hysteroscopy was performed using a 3mm hysteroscope (Stortz) and single channel sheath. Any abnormality (submucous fibroids, polyps, congenital abnormality)

excluded the patient from continuing in the experiment. The cervix was then dilated to size 10 Hegar, and the RF thermal probe placed fully within the uterine cavity until the tip of the probe was at the fundus. A plastic cuscoe speculum was used to avoid the possibility of capacitative drain on the RF thermal probe and possible vaginal heating.

The abdomen was cleaned and draped, and entry to the peritoneal cavity gained via a transverse suprapubic incision. Meticulous haemostasis was achieved using diathermy. The bowel was packed away to leave optimal access to the pelvis. Luxtron probes were then placed using 16 gauge intravenous cannulae (Medicut) as follows, after calibration:

1. Through the myometrium at the level of the mid-body anteriorly, at the RF thermal probe surface (ie. at the point of endometrium/probe interface).

2. As in 1, but withdrawn (using a sterile steel rule to measure) to 5 mm from the RF probe surface.

3. As in 1, but 10 mm from the probe surface.

4. Under the visceral peritoneum in the Pouch of Douglas.

5. Within the uterovesical pouch.

6. Transcervically in the midline anteriorly where the insulated shaft was inserted through the cervical canal. This was to ensure that there was no capacitative heating of the endocervix and therefore bladder.

The 'Kenwood' RF generator set to 27.12 MHz was then connected to the RF thermal probe and the external ground-plane electrode belt via the 'Heathkit' SA-2040 antenna tuning unit (ATU) and power meter. The bowel packs were removed. A period of five minutes was allowed for the Luxtron thermometry probes to equilibrate and achieve a steady reading.

The incident power was then set to 5 W and the SWR tuned to 1.0 by altering the ATU settings, in order to match the impedence load of the thermal probe, patient and belt to the RF generator.

A final safety check was carried out to ensure that the patient was not in contact with any metallic surface, the ECG pads were firmly attached in the correct position (see Section 2 - safety) and connected to the approved ECG monitor via the filter. The automatic BP

monitor (Dinamap) was connected.

The incident power was then increased to 70 W with SWR 1.0 in both patients.

Results

Diagnostic hysteroscopy was normal in both patients. No operative difficulty was encountered at any stage of the procedure, and thermometric probes remained _in situ_ at all times. No difficulty was encountered in tuning the circuit to an SWR of 1.0 in either case.

Baseline temperatures recorded at all points were 35.2 - 36.0 degrees celsius.

No significant rise in temperature was obtained either within the target tissue or non-target tissue after five minutes of RF thermal probe energisation. Skin temperature under the belt electrode remained normal.

Using this equipment it was judged that inadequate power was being provided to create a therapeutic heating effect despite good tuning, and no further

experiments were performed using this set of RF generating equipment _in vivo_.

No intraoperative blood samples were obtained in view of the lack of heating effect.

Conclusions

1. The RF signal generated and tuned using the 'Kenwood' RF generator and 'Heathkit' SA-2040 ATU is inadequate to produce a useful hyperthermic effect within the endometrium _in vivo_, although 70 W of incident power at 27.12 MHz with good tuning (SWR 1.0) was adequate to produce a rise in endometrial temperature of 20 degrees celsius _in vitro_.

2. There is no evidence from these experiments that unwanted heating occurs at this power level, specifically not in bowel, on the bladder surface, in the endocervix or under the electrode belt.

Both patients showed no ill-effects from exposure to RFEM energy intraoperatively. Post operatively both patients remained well, and recovered without

complication. The skin over which the external belt electrode was in contact remained healthy. Follow up in the outpatients department at two and six weeks after operation was unremarkable. All haematological indices were normal and unchanged at six weeks.

Discussion

In view of the highly experimental nature of this work, we did not feel justified in exposing more than a minimal number of patients to each experimental situation. Moreover, it was felt that at this early stage, two patients were sufficient to answer the question of whether the apparatus functioned or not.

Disappointingly, the RF apparatus used for the _in vitro_ experiments failed to produce a useful hyperthermic effect _in vivo_. This was presumed to be due to two factors. Firstly, the cooling effect of the great blood supply to the uterus must have drained away thermal energy deposited into tissues. Secondly, the geometry of the _in vivo_ situation, with a large tissue volume interposing between the thermal probe and the external electrode meant that some proportion of the

incident power was deposited as diffuse heat within those non-target tissues, although despite multi-point thermometry, no such effect could be detected.

In view of the fact that signal power was totally inadequate to produce a useful hyperthermic effect _in vivo_, a linear amplifier was obtained to boost the RF signal for the next experiment.

Secondly, in order to differentiate between loss of heating effect due to blood flow and that due to diffuse deposition of energy in non-target tissue, an experiment was designed to monitor endometrial heating _in vivo_ in the absence of blood flow through the uterus.

5.2 - Intraoperative thermometry at hysterectomy using the linear amplifier for increased RF power, and the effect of uterine devascularisation

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Object:

The purpose of this experiment was to:

1. Test the performance of the RF thermal probe driven by a higher power RF signal using a linear amplifier to boost the output of the RF signal generator.

2. To test the effect on endometrial heating of devascularising the uterus as much as possible, in order to determine if blood flow was the primary cause of failure to heat the endometrium in vivo at 70 W deposited power.

Patients

Entry and exclusion criteria were the same as those detailed in section 5.1.

Materials and Methods

Preoperative assessment of patients and investigations were the same as in section 5.1.

Two patients were selected who conformed to the entry criteria.

Patient Init's	Age	Height (cm)	Weight (kg)	D&C Histology	Day Of Cycle
AS	39	159	85	Benign	12
MD	41	160	69	Benign	14

Both patients gave informed consent after interview with the author, and all investigations (chest X-ray, ECG, haematological parameters) were within normal limits:

Blood results:

Parameter	Patient AS	Patient MD
U&E	Normal	Normal
LFT	Normal	Normal
PT	15 sec	11 sec
PTT	31 sec	28 sec
TT	10 sec	12 sec
[Fib]	3.1g/l	3.0g/l
Free Hb	0	0
FSH	24IU/ml	22IU/ml

The first patient was prepared for theatre, the abdomen opened and the RF thermal probe and Luxtron thermometry probes placed as before.

This time the output of the RF signal generator was connected to the input of a matching 1 kW linear amplifier and the output connected via the ATU to the RF thermal probe and external belt electrode, which was placed around the patients midriff as before. The positioning of the belt was standardised in all patients: the upper margin of the belt was placed at the level of the anterior superior iliac spines.

The incident power was set at 5 W, and the SWR tuned to 1.0. The Luxtron thermometer was allowed to equilibrate and reach steady state after calibration. The incident power was then increased to 450 W, and temperatures recorded.

At the end of a ten minute period, the power was switched off, and the RF thermal probe and belt electrode removed. The uterus was exposed using a self-retaining retractor, and the infundibulopelvic ligaments clamped, divided and ligated using number one chromic catgut. The bladder was then stripped from the anterior aspect of the uterus, and the ureters checked to ensure freedom from the operative field. The uterine arteries were them clamped divided and ligated using the same suture. The retractor was removed, and a complete safety check performed (see section 5.1). The RF thermal probe and sterilised external belt electrode were replaced, and the RF generating apparatus connected and tuned using 5 W of incident power until an SWR of 1.0 was obtained. The RF thermal probe was then energised once again at 450 W, and temperatures recorded.

Blood samples were obtained from a single uterine vein within the broad ligament into a 2 ml syringe via an EDTA flushed epidural catheter. Samples were collected at one minute intervals during treatment, and immediately transferred to paediatric blood count containers.

Results

Diagnostic hysteroscopy was normal in both patients, and no operative difficulty was encountered in either case.

No significant heating was obtained at incident power levels below 300 W. At 450 W a significant rise in temperature was seen at the endometrium and at 5 mm from the thermal probe surface within the uterine wall.

Temperatures within the uterus further than 5 mm from the thermal probe surface and at all extrauterine points remained unaffected by heating.

Temperature rise at the thermal probe surface and at 5 mm in each patient are shown in figure 19 , and after devascularisation are shown in figure 20 (values

averaged for each patient, maximum variation for each reading 1.8 degrees).

It proved technically impossible to obtain uterine venous effluent blood sufficient for coagulation analysis (0.8 - 1.4 ml), but enough was obtained for analysis of red cell morphology. Four specimens were obtained from each patient that were satisfactory for blood films. No red cell distortion was seen in any sample.

Postoperative haematological profiles at six hours and six weeks were normal and unchanged.

Histological examination revealed no abnormality in either specimen, and there was no microscopic evidence of thermal damage.

Both patients remained well postoperatively, and were complication free on discharge one week later. They remained well when seen at follow up one and six weeks later.

Conclusions

1. An incident power of 450 W at 27.12 MHz is sufficient to generate a useful hyperthermic effect _in vivo_, using the linear amplifier.

2. There is no evidence that extraneous heating of non-target tissues occurs at this power level.

3. The average rise in temperature of the endometrium at this power level was increased from 3.6 degrees per minute to 6.0 degrees per minute by devascularising the uterus. Uterine blood flow is therefore a major factor in reducing the thermal effect of applied RF. Haematological examination failed to reveal any heat effects on blood, despite multiple samplings during treatment. Therefore, blood velocity is adequate to preclude any significant heating effects upon blood flowing through the uterus during RF treatment. The major conclusion at the end of this experiment was that the RF apparatus used, with the linear amplifier, had a sufficiently powerful output to justify its continued use in the experimental programme.

The next experiment was designed to 'range' the amount of power needed to achieve a theoretically adequate

thermal dose at the endometrium. This level of incident

power had to fulfil the following criteria:

1. It must be capable of raising the temperature of

the endometrium, taken as the temperature achieved at

5 mm from the probe surface, to a degree compatible

with a histotoxic effect when maintained for a

reasonable length of time. For example, it would be of

little use to raise the temperature to 43 degrees, as

this would theoretically require one hour using the in

vitro model, and even longer in the in vivo situation.

2. The power level must be safe. Very high power

levels may give rise to unwanted RF phenomena, such as

coupling with metallic objects in theatre and charging

them with RF - a potential hazard.

3. The equipment must be capable of 'handling' the

load placed upon it, without overheating, and without

operating at the very limits of its capability, when

spurious variations in power output become a

possibility.

Time From RFTP Energisation (Minutes)
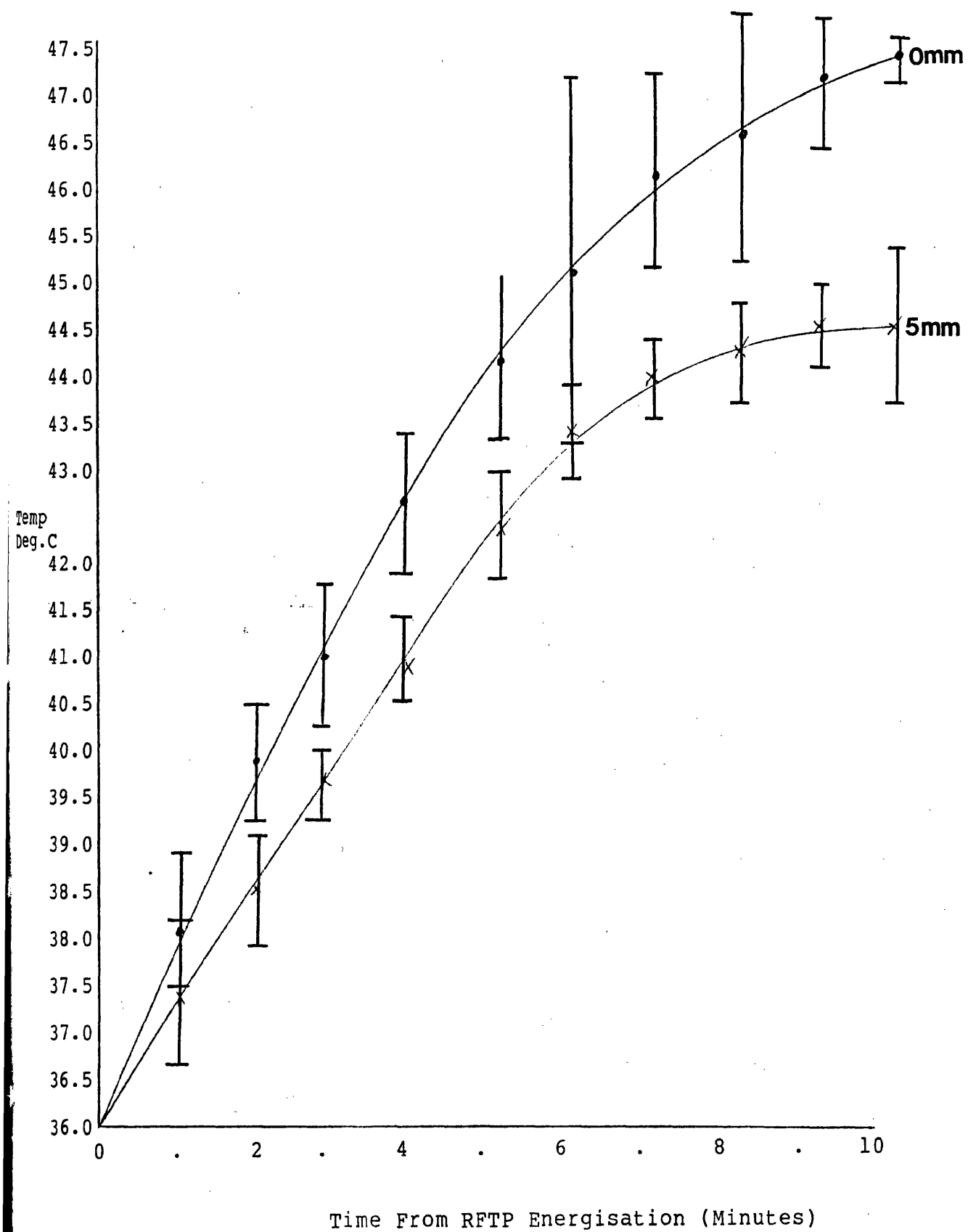
Figure 19: Temperature Rise At 0mm and 5mm From RFTP
With Uterine Blood Supply Intact at 450W Power, 27.12MHz.(n=2)

Time From RFTP Energisation (Minutes)
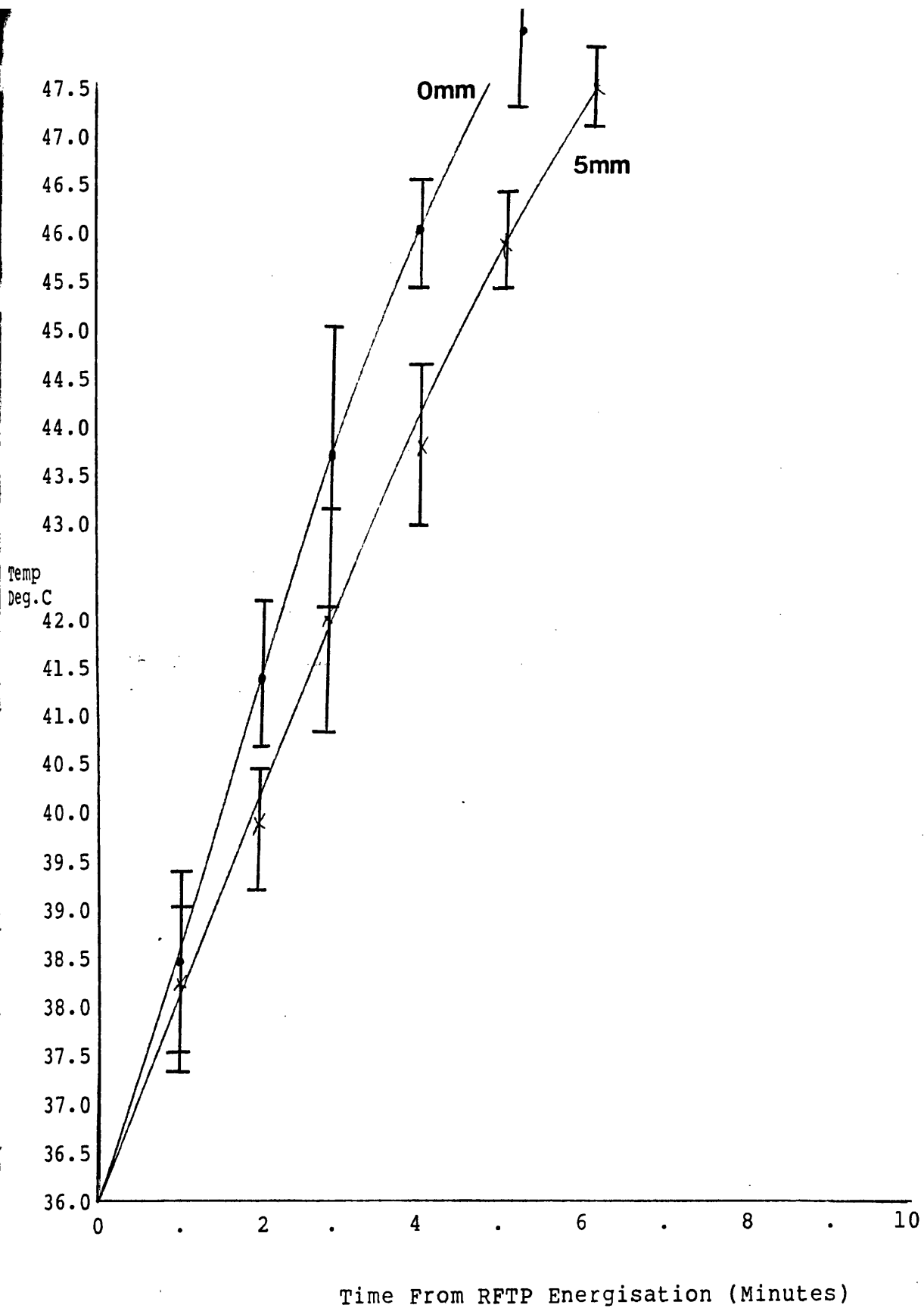
Figure 20: Temperature Rise At 0mm and 5mm From RFTP
After Devascularisation at 450W Power, 27.12MHz.(n=2)

5.3 - Intraoperative thermometry at hysterectomy at 450 - 750 W Incident Power

Object:

The purpose of this experiment was:

1. To treat further hysterectomy volunteers with DUB with full temperature and blood sampling monitoring in order to determine safe temperatures at the endometrium consistent with a histotoxic effect, but without non-target tissue heating (including blood).

2. To determine the final power range for clinical use, consistent with safety, and a therapeutic effect within a reasonable operational timespan (ie. an acceptable clinical treatment time under general anaesthetic).

Patients:

Entry and exclusion criteria were the same as those detailed in section 5.1.

Materials & Methods:

Preoperative assessment of patients and investigations were the same as those detailed in section 5.1.

A total of eight patients were selected who conformed to the entry criteria:

Patient Init's	Age	Height (cm)	Weight (kg)	D&C Histology	Day Of Cycle
RT	41	159	70.5	Benign	16
PS	36	157	67.9	Benign	17
HP	32	154	58.1	Benign	04
BG	50	149	52.0	Benign	21
FK	34	160	67.0	Benign	10
LT	43	159	60.4	Benign	22
JF	38	165	70.6	Benign	12
BS	48	164	79.0	Benign	20

All patients gave informed consent after interview with the author, and all investigations (chest X-ray, ECG, blood pressure and all haematological parameters - see sections 5.1 and 5.2) were within normal limits.

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Each patient was prepared for theatre, a diagnostic hysteroscopy performed, the abdomen opened, RF thermal probe inserted transcervically into the uterine cavity, Luxtron probes placed as in section 5.1, and the RF generating apparatus with linear power amplifier in circuit connected and tuned in the previously described manner.

The incident power was then increased up to 750 W in each patient at 50 W increments for five minutes from 400 - 750 W.

Blood samples were taken via a heparinised syringe and epidural catheter from a single uterine vein in the broad ligament, and submitted for haematological analysis for heat effect.

Results:

Diagnostic hysteroscopy was normal in all patients.

Unwanted RF phenomena were not apparent at 650 W power, but in patient 1, the metallic frame of the operating table became mildly charged with RF at 750 W. The power was immediately switched off, and it was decided

not to exceed 650 W.

Steady state temperatures were achieved for all patients at 450, 500, 550, 600 and 650 W, and these are shown in figure 21. Steady state temperatures at 5 mm depth were between 53 - 54.5 degrees.

RF thermal probe energisation for 20 minutes at 550 W did not cause non-target tissue heating above 39.0 degrees in any patient (figure 22). Temperatures recorded in the endocervical canal (midline, anteriorly, adjacent to bladder) were 37.1 - 38.9 degrees (mean 37.5 degrees) in all cases (figure 23).

Intra-treatment blood samples failed to show any heat effects at 1, 5, 10 and 15 minutes.

No operative difficulty was experienced with any patient, and hysterectomy was uncomplicated. All patients remained well postoperatively, and at follow up one and six weeks later. All haematological and biochemical parameters (see section 5.1) were unchanged and within normal limits.
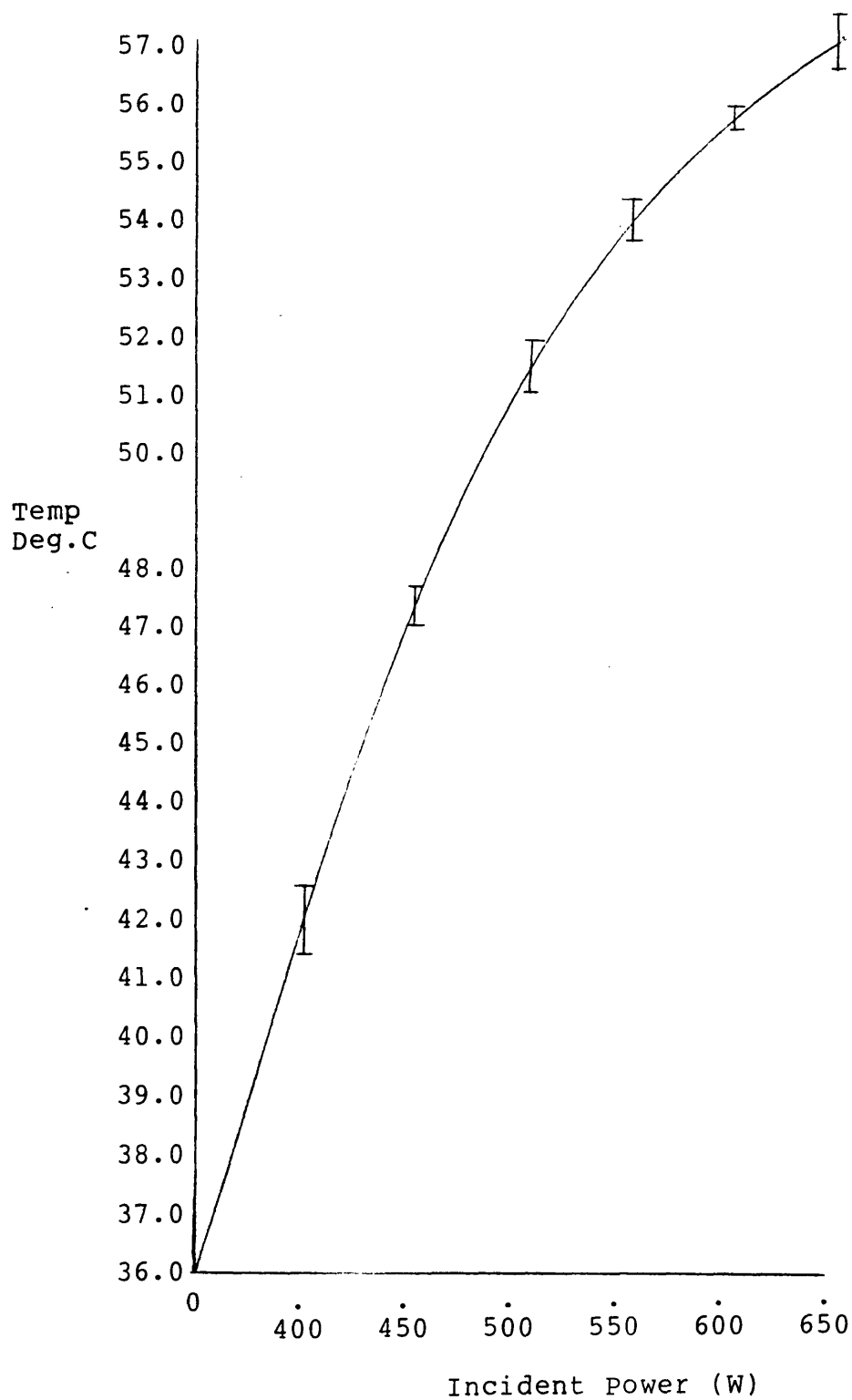
Figure**21** .   Steady State Temperatures
At 5mm Depth As A Function Of Power
(n=4, average values plotted, vertical
bars represent ranges for all patients).
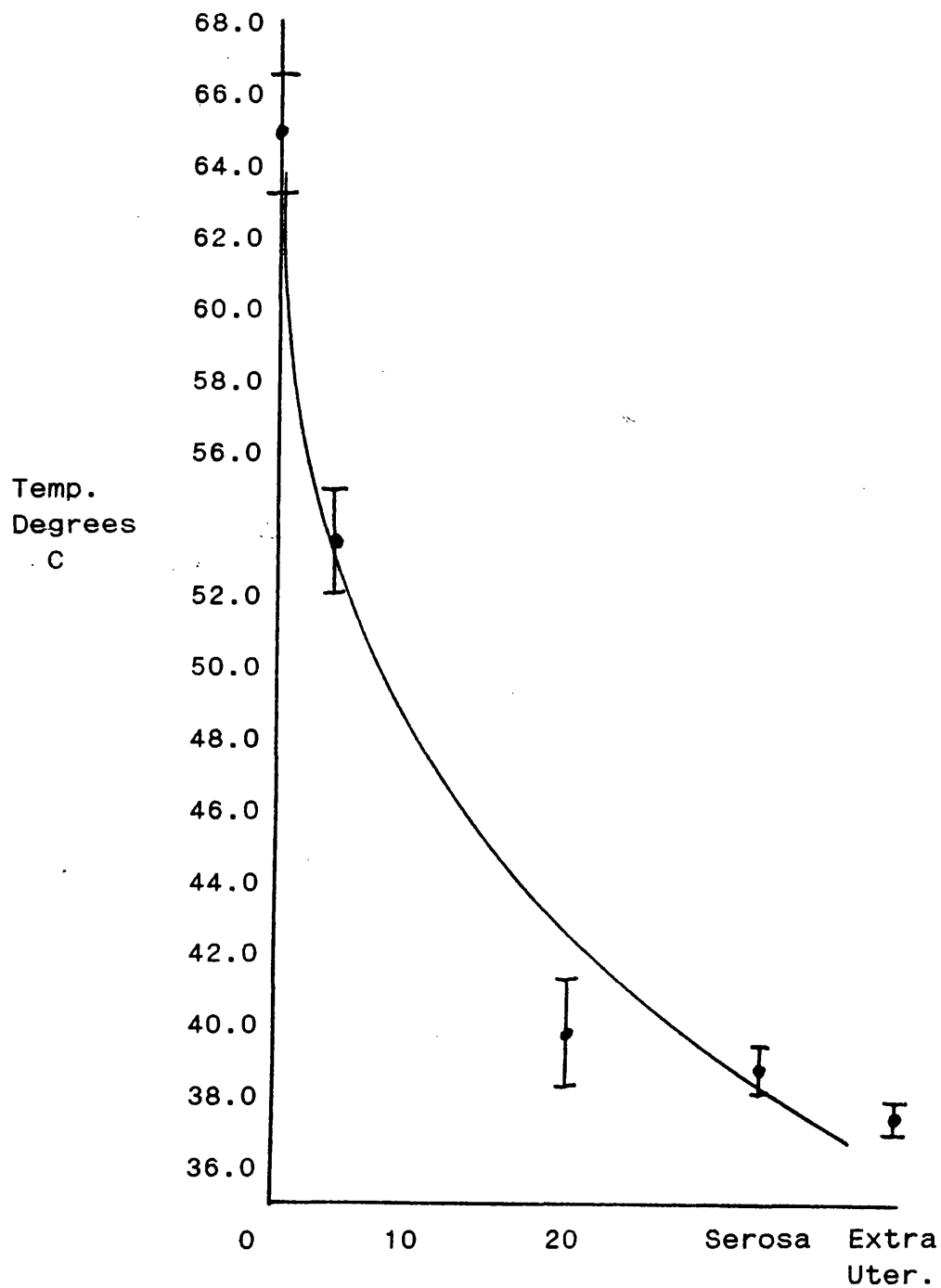
Figure 22. Graphic Representation Of Temperature 'Fall Off' From RF Thermal Probe Surface At 20 mins (n=8, vertical bars represent ranges for all patients)
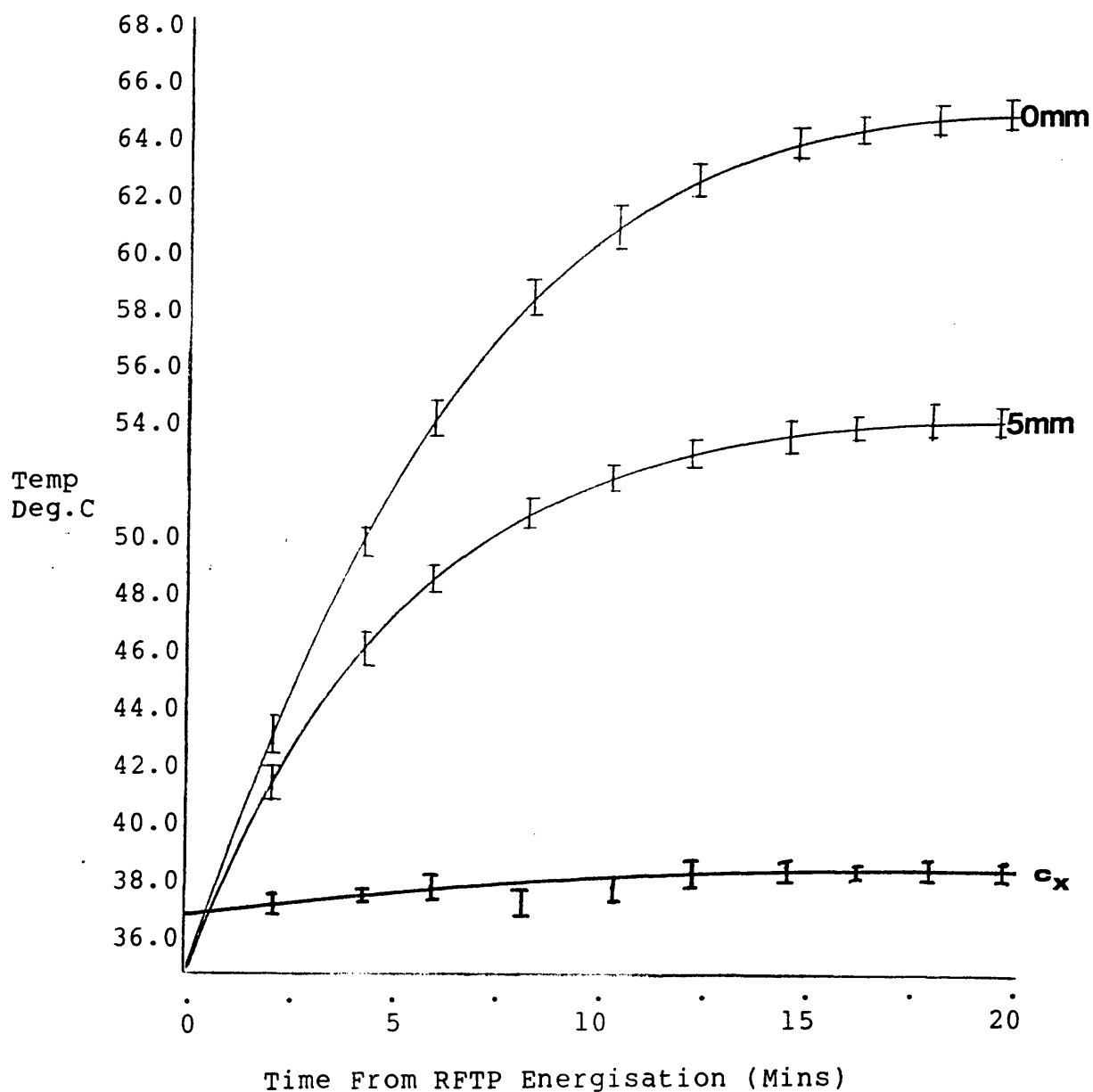
Figure **23** . Temperature At 0mm
And 5mm Depth, 550W Deposited Power
        (n=4, average values plotted, vertical
        bars represent ranges for all patients).

Cx = cervical canal temperature, anterior
midline

Conclusions:

1. 550 W incident power with SWR 1.0 - 1.2 (ie. maximally deposited into tissue as heat) is sufficient RF power to create a useful hyperthermic effect at 5 mm depth within the endometrium, ie. within the tissue volume likely to encompass the bulk of the basalis layer (approximately 53.5 degrees).

2. No unwanted RF effects occur at this power level, and no significant heating of non-target tissues occur.

Discussion:

The most striking feature of the thermometry results is their consistency. Temperatures in all patients at 0 mm and 5 mm varied on average by only 1.4 degrees (S.D. 0.66 degrees). The reasons for this have already been alluded to: relative constancy of the geometry of the thermal probe/patient/electrode belt, and blood supply. Tuning of the circuit also 'equalises' electrical variations between patients.

A useful hyperthermic temperature of approximately 54 degrees at 5 mm depth could be achieved for all

patients using 550 W power. Moreover, we found stray RF effects at around 750 W power, although mild (a 'tingling' sensation on touching the metal frame of the operating table). A safety margin og 200 W is therefore allowed by routinely using 550 W, hence the decision was made to use this as a standard power during treatments.

The next stage was to decide upon treatment time, and therefore thermal dose consistent with safety and efficacy. For reasons already stated, it is not practically possible to demonstrate hyperthermia effects other than by clinical means. The decision was made therefore, to embark upon a clinical trial of 30 patients with the primary aim of investigating possible side effects, ie. toxicity, using thermal doses consistent with an endometrial histotoxic effect, but safely.

Histological Analysis Of RF Ablation Tissue Effects

The initial experimental protocol did include an experiment where patients would receive RF ablation, then undergo hysterectomy one month later (when a

pathological response would be manifest and observable histologically). This created considerable ethical problems, however. Patients would effectively be exposed to an unnecessary general anaesthetic and an unnecessary operation (ie. RF ablation). We did, in fact, find two patients who were willing to participate in such an experiment, who very much wished to know the route of hysterectomy prior to definitive surgery (this could not be judged by prior examination because of minimal uterine descent). In the event, both patients felt that they had derived some benefit from RaFEA, and declined hysterectomy afterwards.

We therefore designed a clinical trial with the aim of ensuring non-toxicity of RaFEA, but also to subjective- ly assess efficacy by recording sanitary protection use and keeping a menstrual calendar before and after treatment.

At 54 degrees the theoretical thermotolerance time of cells is less than a minute, However, we demonstrated that 20 minutes treatment time at 550 W (ie. approximately five minutes 'warm up' time and 15 minutes at 54 degrees at 5 mm depth was well tolerated,

and free from extraneous heating. In hyperthermia, it is usual to give a 'tolerance dose' rather than a dose calculated to theoretically meet the thermotolerance value when deciding the upper dose limit.

Thermotolerances are derived from in vitro cell culture experiments, and thermal doses calculated from these prove inadequate when a volume of tissue is heated in vivo (Hahn, 1982,S.Field, 1989, personal communication). Treatment times of less than 10 minutes were judged highly unlikely to produce an effective endometrial hyperthermic effect.

The explanation for this phenomenon lies in the physical relationship between cells bonded together in tissue, as opposed to cells lying free in tissue culture, on which thermotolerance experiments are largely based. Individual cells in a tissue mass, particularly where there is a large volume blood supply such as that of the uterus, are insulated and hence 'protected' by surrounding cells, interstitia and blood from heating.

During earlier experiments at abdominal hysterectomy,

it was demonstrated that non-target tissue heating
above 39 degrees did not occur at 550 W power. This
was the peak temperature at the serosa of the uterus,
and all other tissues remained at body temperature. It
was therefore felt that this power level was safe, and
we therefore did not vary power when considering
variations of total thermal dose, but rather to vary
treatment time.

Thermal Dose

It is possible to express the hyperthermic dose in
terms of 'equivalent minutes at 43 degrees, (eg. 10
minutes at 46 degrees equals 80 equivalent minutes at
43 degrees). However, this takes no account of 'warm
up' time. One way of expressing the total energy dose
is to use the equation:

Watts x Seconds /1000 = kJ

Thus 20 minutes at 550 W is 660 kJ.

In the following experiment patients were given 330 kJ,
495 kJ or 660 kJ, in order to 'range' the thermal dose
compatible with a therapeutic effect, but also to
monitor subjects for any untoward effects. Patients

were only exposed to the higher doses once it became apparent that there were no serious side effects at the lower doses.

SECTION 6 - IN VIVO HISTOCHEMICAL STUDIES

Object:

The purpose of this set of <u>in vivo</u> experiments was:

1. To ensure that excessive heating and penetration of the myometrium does not occur during RF endometrial ablation, especially with regard to the 'at risk' areas of the uterus where the myometrium is thinnest (Langois, 1970, Markee, 1966), ie. at the cornua, isthmus and cervix, where it may be as thin as 7mm.

Patients

Entry and exclusion criteria were the same as for Section 5 - <u>In vivo</u> thermometry studies. Ethical committee approval was obtained. Haematological and biochemical profiles (as in section 5) were all within normal limits. FSH levels were premenopausal (<30 IU/ml).

Materials and Methods

Under general anaesthetic, each patient was cleaned, draped and catheterised. The external belt electrode

was fitted around the patients waist, and a full safety check carried out (patient not touching metal, ECG filter in line, BP cuff connected). The cervix was dilated to size 10 Hegar, and the length of the canal measured with a uterine sound. Ultrasound measurements were consulted, and an appropriate length probe selected. The thermal guard was fitted and the cervix locked in using two stay sutures. The probe was fully engaged. The belt and probe were connected, and a baseline temperature noted within the cavity using the built-in thermometry probe and monitoring circuitry. The generator/probe/patient circuit was tuned to an SWR of 1.0 using a signal strength of 10 W, and then a full power signal of 500 W applied to the probe. Probe temperature was maintained at 60 +/- 2 degrees celsius for 15 minutes.

After RF treatment, a routine abdominal hysterectomy was performed via a Pfannenstiel incision in each case.

First, in order to assess tissue shrinkage due to loss of turgor from blood supply and histological processing, two parallel incisions were made in each uterus in the saggital plane in the midline on the

fundus of each specimen to a depth of 1mm. Two scalpel

blades set 10mm apart on a steel spacer were employed.

The distance between these marks was subsequently

measured after preparation, and the percentage tissue

shrinkage calculated.

The operative specimen was transferred immediately to

the   pathology   laboratory, and wedge sections   of

endometrium   and   myometrium   taken   from   the   sites

described in Section 4 - _in vitro_ Studies (ie., the

isthmus, mid-body, ostia (coronal), ostia (saggital),

fundal (saggital), with the addition of sections from

the cervical canal (saggital and coronal) .   Frozen

sections were prepared from each, then stained in all

cases with both H & E and for active/inactivated G6PDH

(for technique, see Appendix 3, Bancroft and Hand,

1987).

Patient Details:

Patient Init's	Age	Uterus Dimen. (mm)	Cavity Length (mm)	Previous Histol'y	Day Cycl
1. PT	43	104x70	80	Benign	13
2. LF	37	120x70	74	Benign	16
3. HO	48	100x87	84	Benign	?

? = Day of cycle unknown (erratic bleeding)

Results

Endometrial ablation and subsequent hysterectomy were carried out without difficulty. The only feature noted in the pelvis was some hyperaemia of the uterus, but there was no evidence of extrauterine probe or thermal penetration, especially at the cornua. Patients recovered uneventfully in all cases, and were well at one and six week follow up. Haematological and biochemical indices were unchanged and within normal limits. FSH levels were within the premenopausal range in all three patients at six weeks and three months postoperatively.

Uterine Morphometry:

Patient	Endometrial Thickness (max, mm)	Myometrial Thickness(mm)						
		Is	MB	OC	OS	FS	CC	CS
1. PT	5.6	9	31	10	9	29	15	15
2. LF	6.0	11	28	14	10	40	17	18
3. HO	4.0	20	40	11	12	37	20	20

* Is = posterior isthmus

  MB = mid-body

  OC = ostia, coronal section

  OS = ostia, saggital section

  FS = fundus, saggital section

  CC = cervix, coronal section

  CS = cervix, saggital section

Tissue Shrinkage

The 10mm apart marks on the three specimens were, respectively, measured at 9mm, 8mm, and 8mm for patients 1, 2 and 3, ie. an average shrinkage of approximately 18%.

H&E routinely fixed sections showed no significant

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feature, specifically no evidence of tissue damage. This is not surprising, since there are no histological markers immediately after hyperthermic tissue damage (tissues may in fact be fixed by heating to 65 degrees celsius by microwave oven for histological analysis). See figures 24, 25).

Histochemical Findings

There was no evidence of G6PDH denaturation in any section from any of the three specimens (see figures 26, 27).

Conclusions

The results from this study confirm that intracellular heating does not occur to an extent where cellular enzyme denaturation is manifest, ie. over 60 degrees celsius (McKenzie, 1983). The histotoxic effect relies upon the principle of hyperthermic cellular damage, ie. initially by damage to cytoskeletal proteins. Specifically, there is no evidence to suggest that there is excessive heating of the thin areas of the uterine wall at the cornua, isthmus and cervix.

Figure **24** . Low power section of fundal endometrium

after RF endometrial ablation. (H&E)
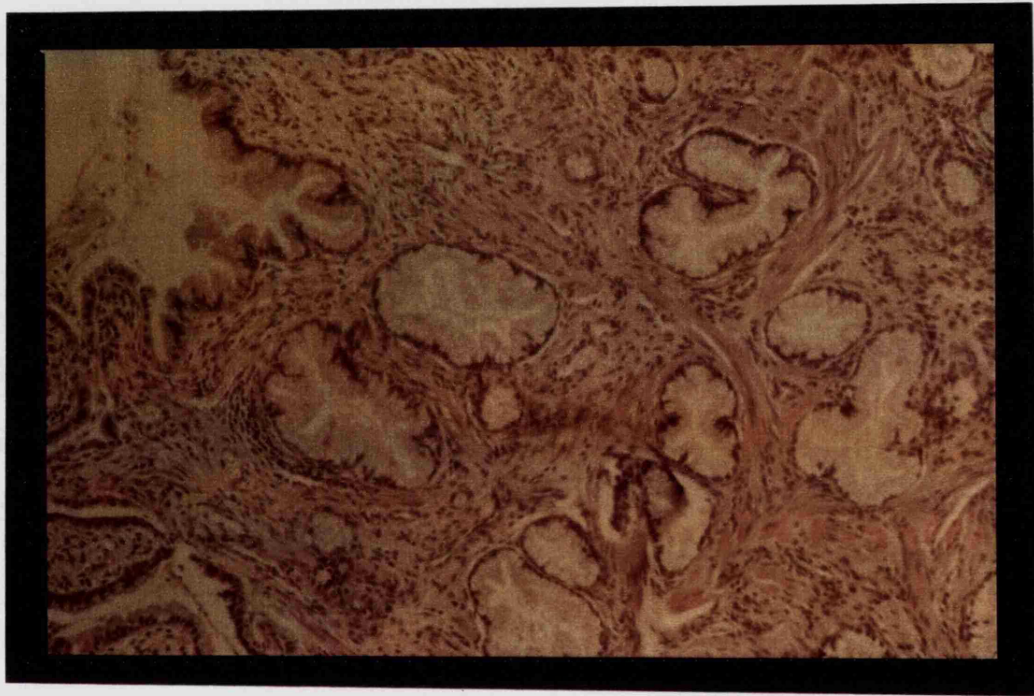
Figure **25** . High power section of endometrial surface from mid-body after RF endometrial ablation. No markers of tissue damage are seen. (H&E)
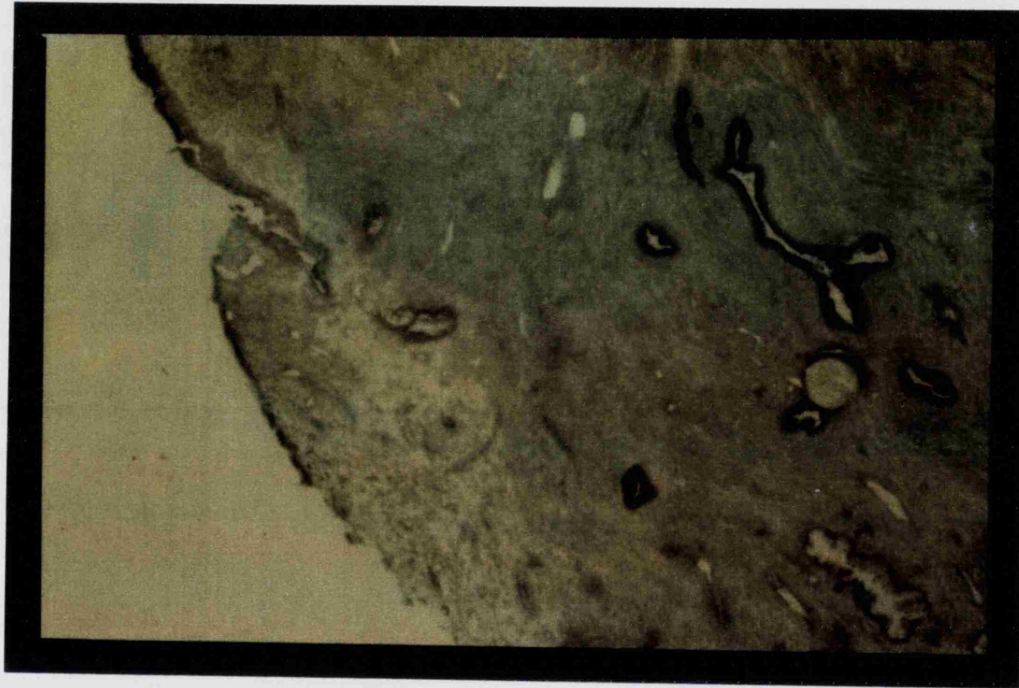
Figure **26** . Section of isthmic endometrium after histochemical staining. All of the tissue showed a positive reaction for the presence of G6PDH.

Figure 27. Section of cervical canal/isthmic junction after histochemical staining. The tissue showed a positive reaction for G6PDH uniformly.

Figure 29 .   Low power section of proximal cervical

canal/isthmic junction, showing no recognisable markers

of tissue damage. (H&E)

SECTION 7 - CLINICAL PILOT STUDY

This was a clinical trial of 30 patients, treatment dose 330 kJ, 495 kJ or 660 kJ (550 W deposited power, equivalent to maximum basalis temperature approximately 54 degrees celsius).

Object:

The purpose of this experiment was:

1. To closely monitor patients during and after RaFEA, but without intra-abdominal thermometry.

2. To discover any short- or medium-term side effects.

3. To determine, In a non-objective way (at this stage) efficacy of various doses of thermal energy at 550 W deposited power (ie. basalis temperature approximately 54 degrees). However, this was not the primary objective. Accurate objective studies of blood loss were performed in the following section using radioactive iron assay.

Patients:

The admission criteria were:

1. Patients gave informed consent after detailed

explanation by the author.

2.   A diagnosis of primary intractable DUB   was   made,
and patients fulfilled the following criteria:

i.   Blood clots were passed per vaginum for 24 hours or
more.

ii.   A total of ten or more towels or tampons were used
in any 24 hour period, and towels or tampons were
changed because of saturation or near-saturation, and
no other reason (ie. not changed according to time
interval or routine).

iii.   The patient felt that her periods were signifi-
cantly abnormally heavy.

3.   Patients agreed to keep a detailed menstrual
calendar for one cycle before RaFEA therapy and two
cycles afterward.

4.   They had finished their families (patients were
warned that RaFEA may well affect fertility).

5.   A diagnostic curettage and hysteroscopy had shown
normal histological analysis of any curettings within

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nine months of RaFEA.

6. They were aged between 35 and 55 years.

Patients were excluded from the trial if:

1. They failed to fulfil any of the entry criteria.

2. They suffered from any serious intercurrent medical condition, including severe obesity. Previous anaemia secondary to menorrhagia did not exclude patients from the trial, but this was corrected by transfusion two weeks prior to treatment.

Materials & methods

The RF generating and tuning apparatus, RF thermal probe and external electrode belt were used as before.

The luxtron electronic thermometer was used with a single probe at the probe/endometrium interface transcervically in order to monitor maximum temperature generated.

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Patients were assessed by an anaesthetist preoperative-
ly and judged fit (ASA I). A light general anaesthetic
was administered (propofol intravenous injection, ICI)
and placed in the lithotomy position. After cleaning
the vagina with aqueous antiseptic solution, the os was
dilated to size 4 Hegar, and a diagnostic hysteroscopy
performed, and the depth of the cavity measured.
Normality of the cavity was a prerequisite to
continuing the treatment. The RF thermal probe was
placed fully within the endometrial cavity under direct
hysteroscopic control, and the hysteroscope withdrawn.
Each patient had had the external 'belt' electrode
placed around the abdomen prior to anaesthesia.

The circuit was tuned to an SWR of 1.0 using 5 W
incident power, then power increased to 550 W, and
remained energised for either 10, 15 or 20 minutes.

Endometrial temperature was continuously monitored and
recorded.

After treatment, patients were recovered and observed
in the day case ward for eight hours. They were then
reviewed at 48 hours, one and two weeks, and at one

month intervals for eight months postoperatively.

Full haematological and biochemical profiles were taken
before treatment and at six weeks postoperatively,
including FSH (see section 5), all results were within
normal limits and were unchanged after therapy.

Patient Init's	Age	Height (cm)	Weight (kg)	D&C Histol.	Day Of Cycle	Treatment Dose (kJ)
01.LM	46	163	81.4	Benign	17	330
02.PH	51	158	62.7	Benign	-?*	330
03.LH	37	152	64.8	Benign	23	330
04.PB	39	149	58.9	Benign	05	330
05.HP	49	159	80.6	Benign	25	330
06.JT	51	151	59.7	Benign	17	330
07.RS	47	160	71.0	Benign	02	330
08.PJ	38	165	90.4	Benign	18	330
09.GB	51	170	88.7	Benign	19	495
10.JM	36	163	72.0	Benign	-?*	495
11.FH	48	164	110.5	Benign	03	Failed
12.BV	49	168	78.5	Benign	17	495
13.KM	35	162	59.0	Benign	12	495
14.VI	51	148	49.0	Benign	18	495
15.DO	41	163	109.1	Benign	09	495
16.NR	55	170	89.1	Benign	19	495
17.HW	42	169	78.9	Benign	09	495
18.GE	52	153	61.9	Benign	-?*	495
19.GL	41	?+	?	Benign	30	495
20.UM	36	?+	?	Benign	27	495

Patient Details:

Patient Init's	Age	Height (cm)	Weight (kg)	D&C Histol.	Day Of Cycle	Treatment Dose (kJ)
21.RM	45	153	72.4	Benign	12	660
22.VN	38	161	66.9	Benign	11	660
23.FO	42	151	78.8	Benign	13	660
24.JH	38	146	61.9	Benign	11	660
25.JE	46	148	61.6	Benign	16	660
26.TK	41	158	61.7	Benign	13	660
27.HE	47	152	62.9	Benign	06	660
28.YV	36	155	73.4	Benign	14	660
29.KR	46	159	69.7	Benign	15	660
30.HQ	35	164	67.0	Benign	11	660

* = erratic cycle   + = Height/weight not recorded

Failed = technical failure of apparatus (Patient 11 too obese for external belt electrode to encompass abdomen).

Results:

No difficulty was encountered with any patient with respect to tuning or delivery of RF thermal energy, except for patient 11, who was too obese to allow placement of the external belt electrode. RF thermal probe insertion was uncomplicated in all other cases. Patients 4, 7 and 10 were menstruating at the time of operation. In the first of these cases (patient 4) it was found that despite the fact that the RF thermal probe was firmly in contact with the cervical os, some blood did escape and lie in the vault just before treatment was about to begin. It was felt that this added another variable which should be excluded, since under these conditions a body of (highly conductive) blood clot would be in the immediate vicinity of the active end of the thermal probe and theoretically might affect tuning during treatment, or possibly be subject to unwanted heating, although the latter was considered unlikely. Moreover, actively bleeding endometrium is likely to be highly resistant to thermal damage because the high specific heat of water in blood would cause poor heating of the underlying tissue, and effectively insulate the 'target'. On these grounds it was

decided to exclude this potential variable from the experiment.

In the remaining 26 patients, diagnostic hysteroscopy was normal in all cases.

Side Effects:

In one patient considerable difficulty was experienced in retracting the vagina from the operative field (patient 15) with the plastic cuscoes speculum, and the vagina was in point contact with shaft of the thermal probe anteriorly. Later analysis also showed that the probe shaft was faulty in that the central conducting core had 'migrated' from the centre of the nylon shaft to the outside (although not quite visible, and hence undetected). This lead to vaginal heating and a vesico-vaginal fistula, which was subsequently repaired without further complication. A further case of fistula occurred which was delayed in presentation because the general practitioner mis-diagnosed stress incontinence. Again, the faulty prototype probe and poor surgical access were implicated (see section 2 - safety). This was also repaired without further

difficulty. Both patients are well and asymptomatic 18 months later, and are both amenorrhoeic.

Most patients suffered some degree of lower abdominal pain for up to five hours postoperatively. In 5/26 this required parenteral opiates for the first few hours, but all but one patient were treated as day-cases. One patient required overnight stay for pain control, but was discharged the following day symptom-free. The pain resolves after a few hours usually, to be replaced by a dull ache which may last for several days. 24/26 patients had returned to work within 10 days.

All patients had some degree of bleeding after treatment. In 20/26 this was light and settled after one week.

Three patients bled for 10 -14 days after treatment, but never more heavily than a normal period, and no active measures were required. One patient bled for four weeks, with passage of clots for two weeks after RaFEA. She was treated with cyclokapron (GP), and settled thereafter.

All patients received metronidazole 200 mg TDS and cephradine 250 mg QDS for two weeks after therapy as a precaution against infection of necrotic tissue. No patient suffered any genital tract infection, and MSU at one and six weeks postoperatively were sterile.

Follow Up

Clinical examination of all subjects was normal at one, six and 12 week follow up and all were well. Patient 15 who developed the fistula defaulted. Haematological and biochemical parameters were normal and unchanged at one and six weeks after treatment (as section 5), and FSH levels were in the premenopausal range (< 30 IU/ml).

Equipment Performance

An endometrial surface temperature of 64.0 - 65.5 degrees was achieved in all cases, consistent with a 5 mm depth temperature of approximately 54 degrees.

Effect On Menstrual Loss

Since no objective studies of menstrual blood loss were performed in this experiment, no firm conclusions may be drawn from these results, although all patients agreed to keep an accurate menstrual calendar, and agreed to change tampons or towels when near saturation, rather than according to a time schedule.

However, since menorrhagia is a subjectively interpreted condition, it seems appropriate to assess the patients own perception of benefit or otherwise.

Figures 30 - 35 show the subjective effect of RaFEA at the three doses of energy used for each individual patient. The numbers are too small and the data too 'soft' to perform meaningful statistics; this was primarily a study of safety and patient acceptability. It was therefore necessary to plot the result of each individual patient.

A dose of 330 kJ resulted in a significant reduction in menstrual loss in two patients, both in number of pads/tampons used per 24 hours when flow was heaviest

and number of days of bleeding. Both patients judged treatment a success and after six cycles did not request further treatment. The remaining four judged therapy a failure; two asked for further RaFEA, and two declined further treatment. Neither came to hysterectomy, however.

495 kJ produced a 'cure' in 5/9 patients, who were satisfied that their menorrhagia had been dealt with. All four of the remaining patients elected for further ablation.

Of the 10 patients who received 660 kJ, three were amenorrhoiec after six cycles, and 8/10 judged therapy a success. With this dose, those still menstruating reported a much greater reduction in flow compared to the majority of patients who received the lower doses. The reason for failure of therapy in 2/10 is unclear. Both requested repeat treatment.

Patient Characteristics

The numbers involved in this pilot study are too small to analyse statistically, and there is no obvious
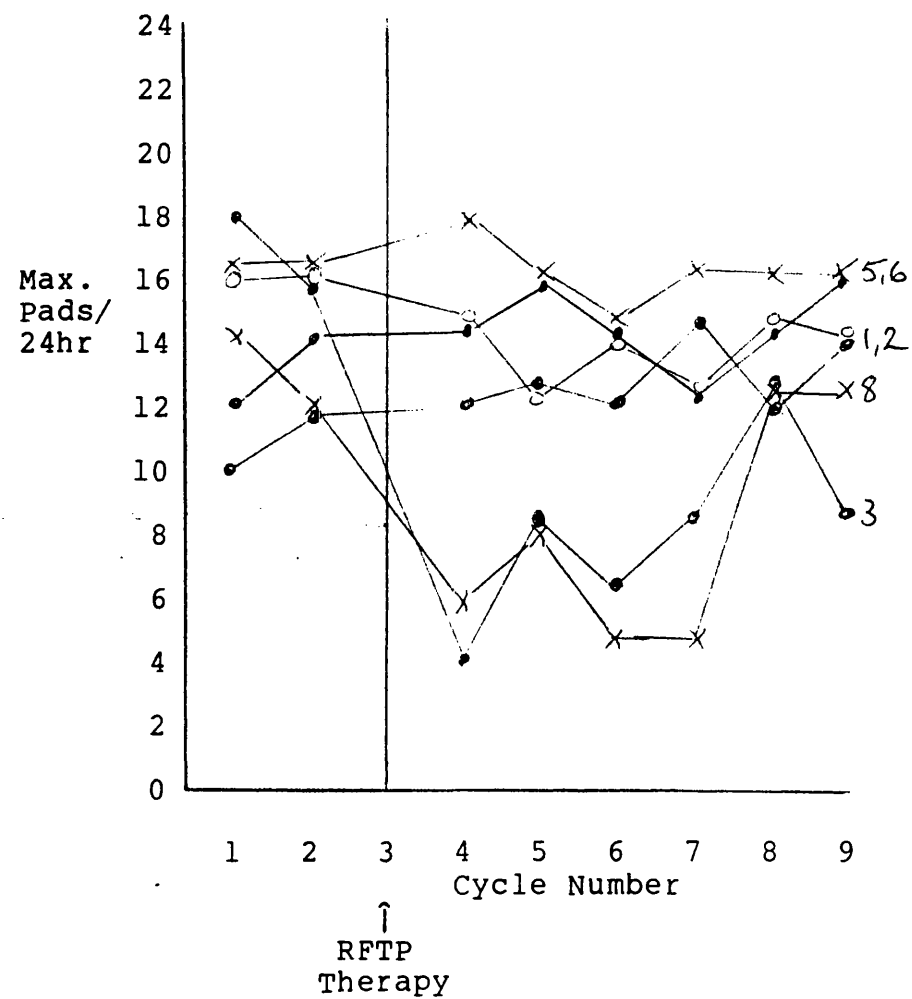
Figure 30 . Effect Of 330kJ Thermal Dose On Subjective Menstrual

Loss In Terms Of Maximum Number Of Pads/Towels Per 24hr

Figures on right refer to patient number
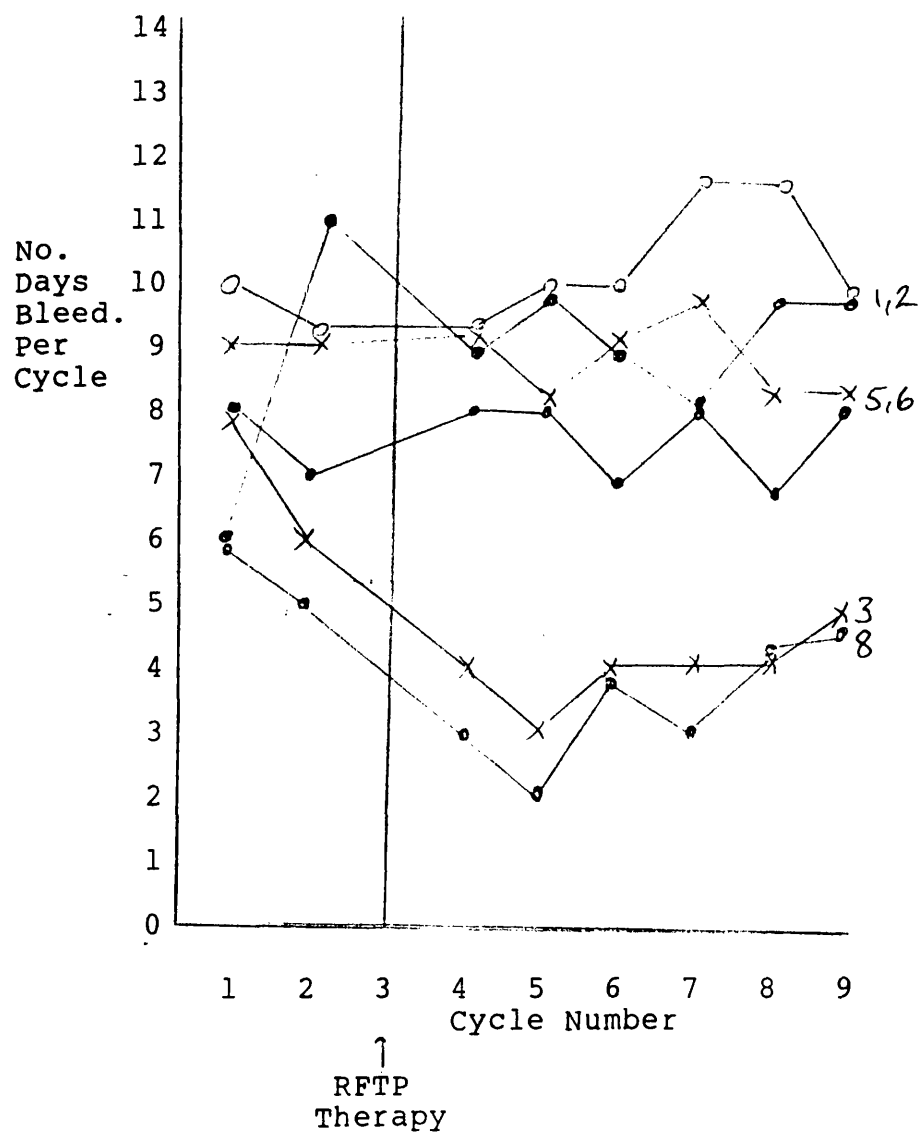
Figure 31. Effect Of 330kJ Thermal Dose On Subjective Menstrual

Loss In Terms Of Number Of Days Bleeding Per Cycle

Figures on right refer to patient number.
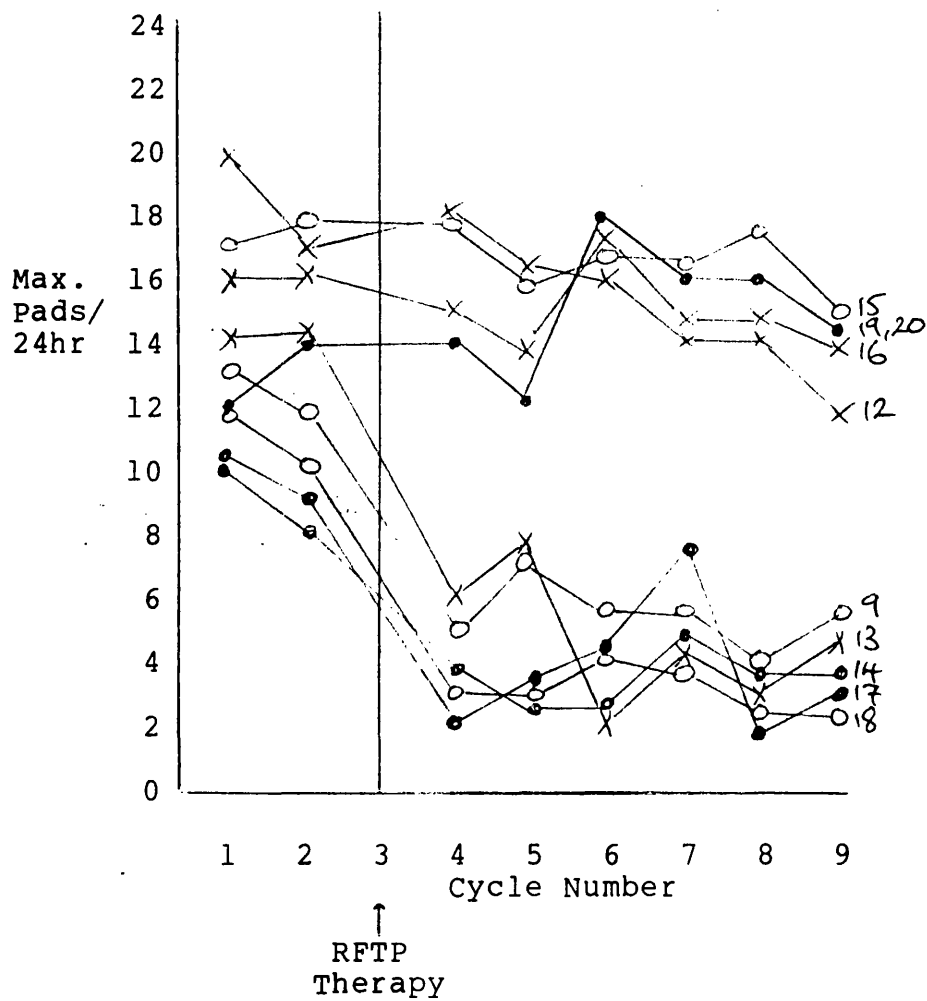
Figure 32 . Effect Of 495kJ Thermal Dose On Subjective Menstrual

Loss In Terms Of Maximum Number Of Pads/Towels Per 24hr

Figures on right refer to patient number
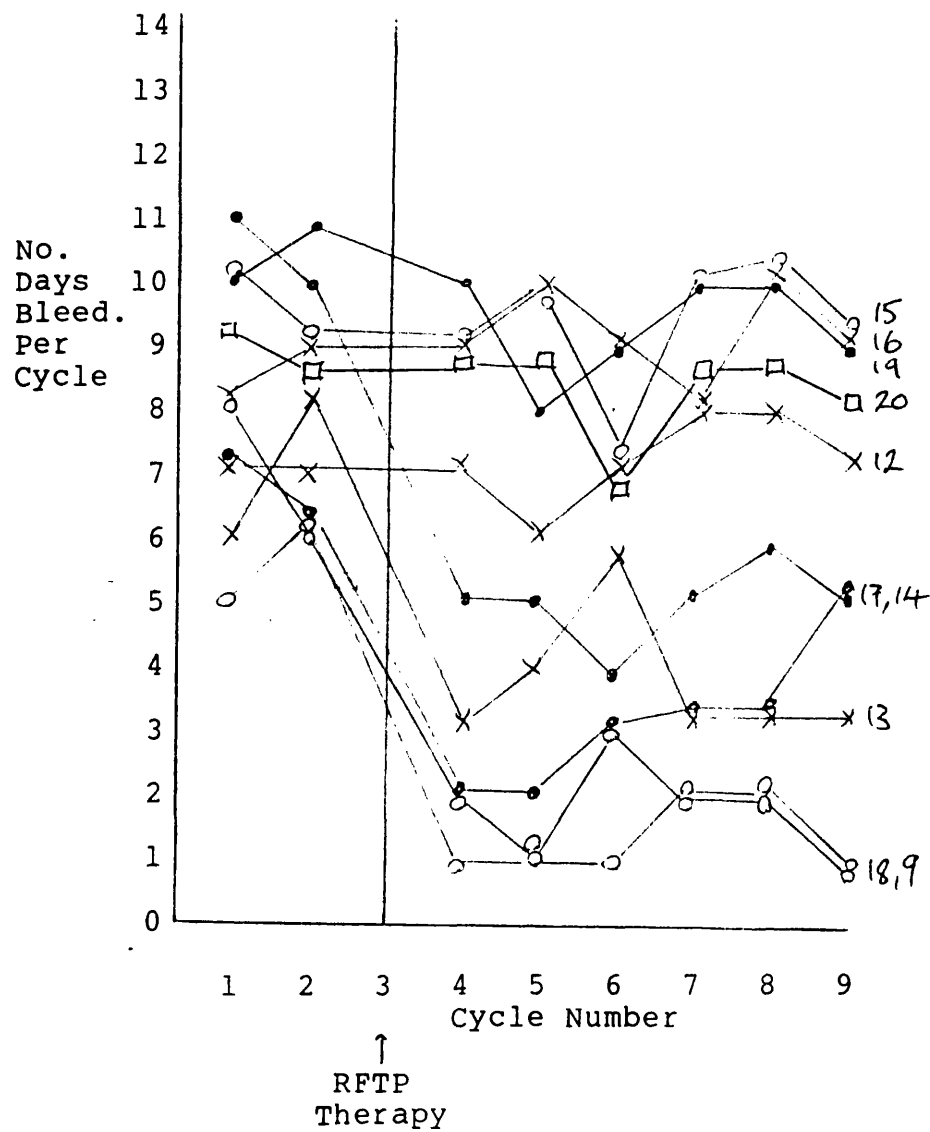
Figure 33 . Effect Of 495kJ Thermal Dose On Subjective Menstrual

Loss In Terms Of Number Of Days Bleeding Per Cycle

Figures on right refer to patient number.
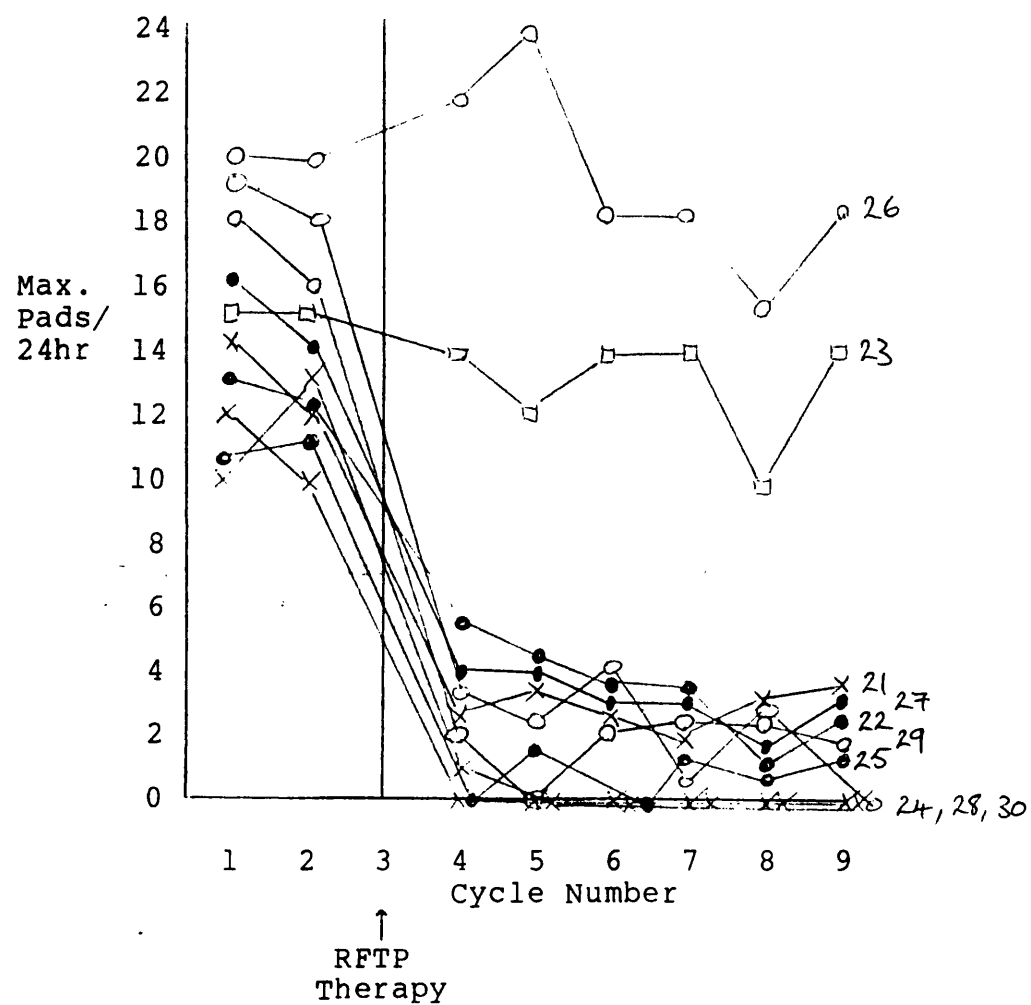
Figure 34. Effect Of 660kJ Thermal Dose On Subjective Menstrual
Loss In Terms Of Maximum Number Of Pads/Towels Per 24hr

Figures on right refer to patient number
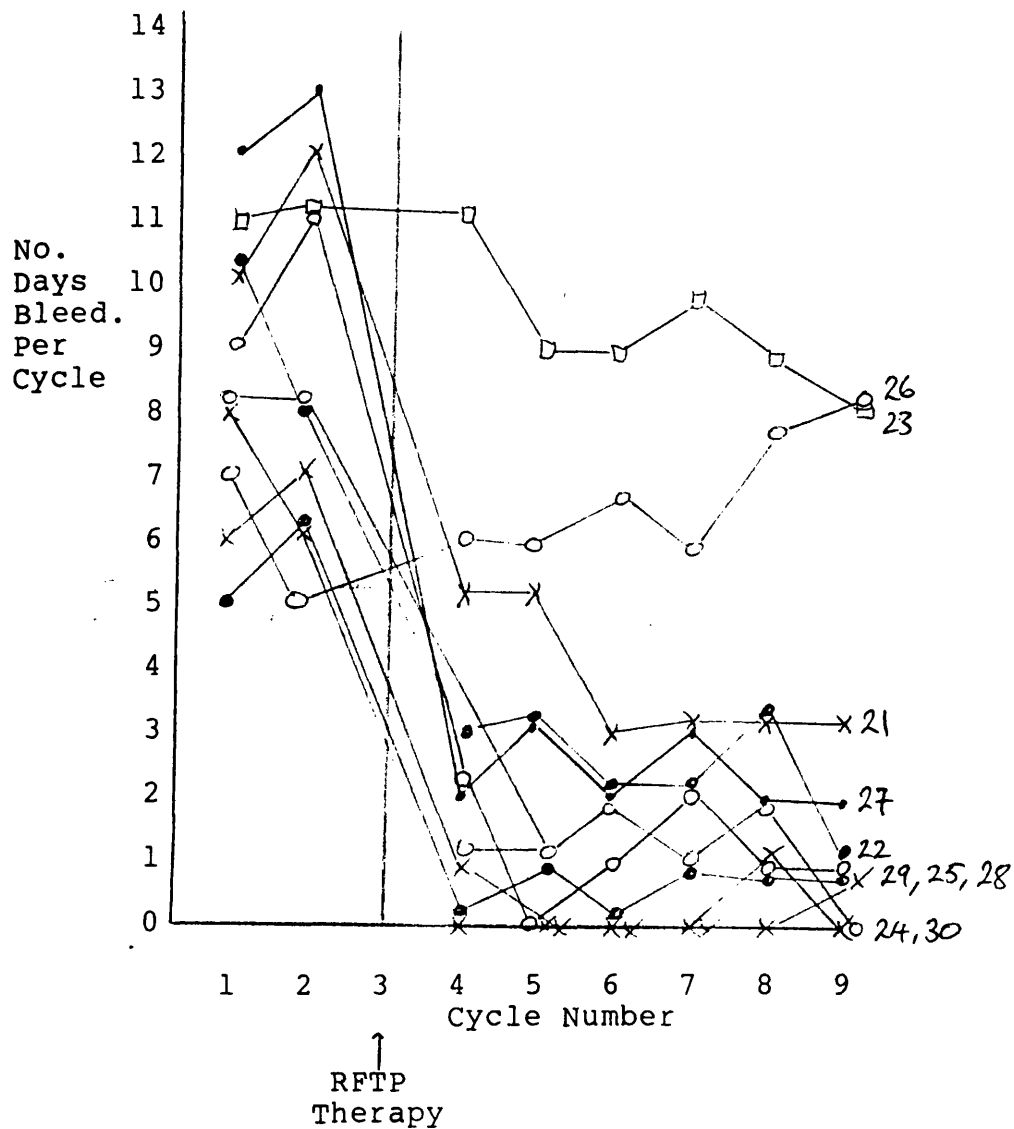
Figure 35. Effect Of 660kJ Thermal Dose On Subjective Menstrual

Loss In Terms Of Number Of Days Bleeding Per Cycle

Figures on right refer to patient number.

effect of age, height, weight or day of cycle when treated on outcome. There was no significant difference in these parameters between the different dose groups, which might otherwise create a bias.

Post Ablation Hysteroscopy

Three patients (two amenorrhoiec and one hypomenorrhoiec) agreed to undergo hysteroscopy several months after ablation. These were patients 18 (495 kJ, hypomenorrhoiec), 24 (660 kJ, amenorrhoiec) and 30 (660 kj, amenorrhoiec). Photographs are shown in figures 36 - 38.

Unfortunately, there was a technical problem with the photographic equipment for patient 24, and only half the optical field is shown. It was not considered acceptable to repeat the procedure, however.

The picture of patient 18 shows a fibrous cavity free of viable endometrium except at the cornua, which accounts for continued, although greatly reduced, menstruation. The defective picture of patient 24 is a poor representation of the hysteroscopic findings,
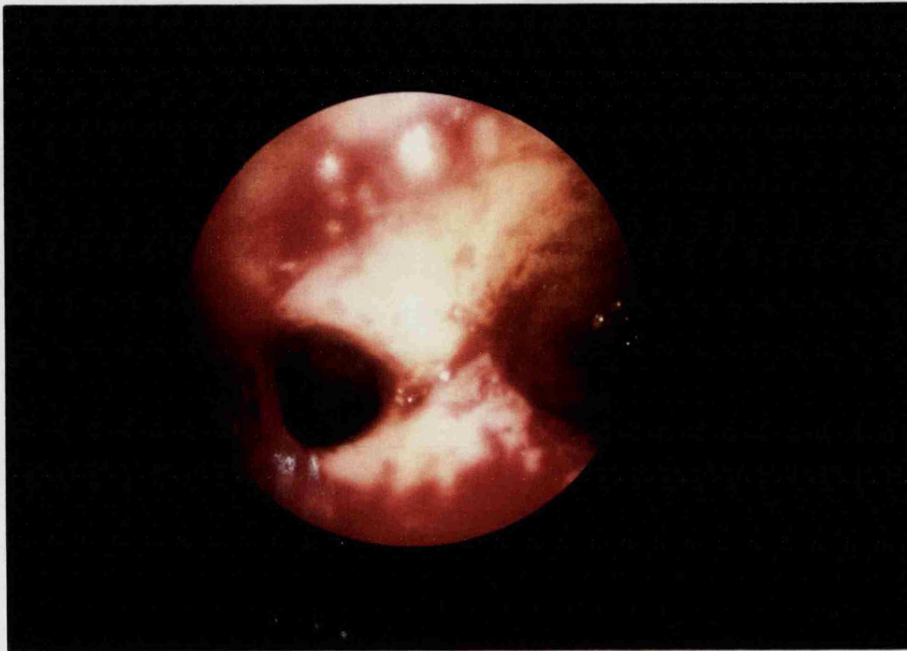
Figure 36 . Hysteroscopic photograph of patient 18, four months after receiving 495kJ (hypomenorrhoeic). The majority of the cavity is replaced by white fibrous tissue, but the cornua retain the pinkish appearence of viable endometrium.

Figure 37 . Hysteroscopic photograph of patient 24, five months after receiving 660kJ (amenorrhoeic). Photographic technical fault. The entire cavity was replaced by fibrous tissue. In the photograph, only a limited area of one of the cavity side walls may be seen.
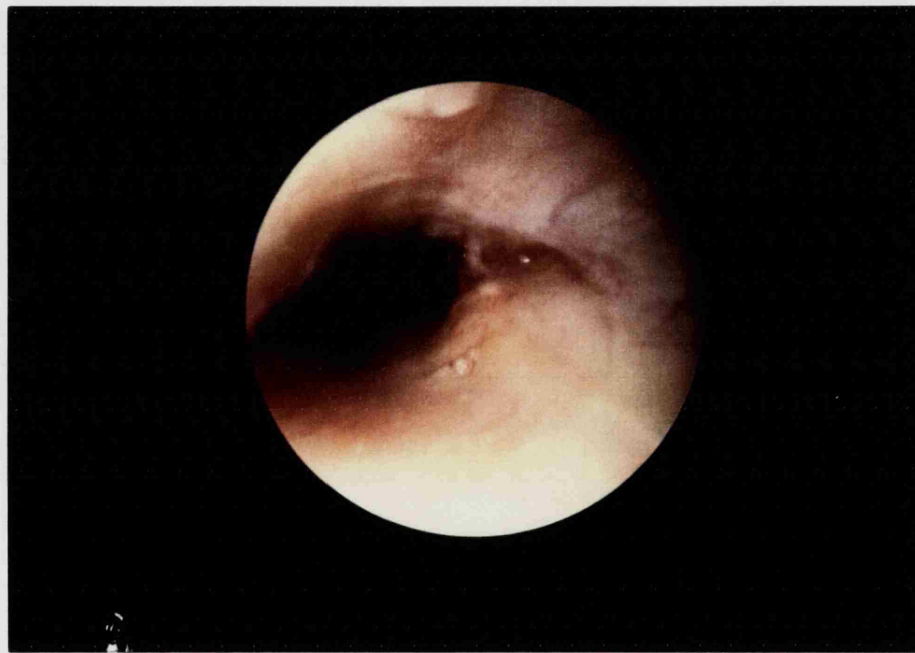
Figure 38 .   Hysteroscopic photograph of patient 30 ,

five months after receiving 660kJ (amenorrhoeic).   The

cavity is entirely denuded of endometrium, and appears

white. A complete view of the cavity is seen here from

the lower limit of the isthmus upwards. The cornua are

in   shadow, but no viable endometrium   could   be

visualised.

which showed a completely fibrotic cavity (but no intrauterine synechiae). The picture of patient 30 shows again a completely denuded cavity, entirely replaced by fibrous tissue.

Transcervical biopsies of the cavity wall confirmed only fibrous tissue on histological examination.

Vabra aspiration biopsy

This was performed on all patients who received 660 kJ (except those who agree to hysteroscopy). Even in those patients who experienced hypomenorrhoea, and were at mid-cycle at biopsy, no viable endometrial tissue could be obtained. The reason for this was presumable because any remaining endometrium was high in the cornua, and inaccessible to the aspirator.

Discussion

Safety

At this stage some 40 patients had been exposed to RaFEA, and one had developed a fistula, although there

were no other types of complications, especially burns at any remote site. Meticulous care with prevention of earth contact and monitoring equipment filtering prevented such complications (see section 2 - safety).

The problem with intrusion of the vaginal wall was overcome with the development of the thermal guard (see section 1 - equipment design and development). To date there have been no further cases of bladder damage where the thermal guard has been <u>placed and maintained in position correctly</u>.

Effect Of Cycle Day/Endometrial Thickness

In order to maximise the therapeutic effect, it may be ideal to treat when the endometrium is at minimal thickness, ie. when the basalis layer is 'maximally exposed'. Patient numbers in this small series were too small to perform meaningful statistics, and the measure of efficacy was a subjective one. The effect of cycle day at operation was therefore impossible to determine from this study. This would require a large scale clinical study, and would be part of a future development project.

A thermal dose of 660 kJ was well tolerated and judged safe (see above; excluding the case of fistula which was due to a proven double technical fault) and effective. We therefore used this dose for the study of effect on objectively measured menstrual blood loss.

SECTION 8 - MEASUREMENT OF MENSTRUAL BLOOD LOSS   BEFORE
AND AFTER RF ENDOMETRIAL ABLATION

Object

This was a pilot clinical trial of 15 patients   treated with   RaFEA   (endometrial surface temperature   60   +/-5 degrees for   15 minutes).   Menstrual   blood   loss   was measured   for two cycles before and after treatment   by radioactive iron (^{59}Fe) injection and whole-body   gamma counting.

The purpose of this experiment was:

1.   To   objectively confirm the   clinical   results   of section   7,   that   RaFEA is effective   in   reducing   or stopping menstrual blood loss (MBL).

A   DoH   license   was   obtained   which   allowed   the administration of ^{59}Fe to 20 patients only.   Recruiting was   difficult,   however,   because the protocol   required six visits to Northwick Park Hospital Clinical Research Centre   (for whole body gamma counting).   15   patients were   successfully   admitted   and   completed   the experimental protocol.

Patients

The same criteria for admission to this trial applied as those for section 7, with the additional consent of the patients to participate in blood loss studies. Exclusion criteria were also the same as those for experiment 5. Haematological and biochemical indices were within normal limits (except for two patients who were anaemic; other parameters within normal limits). Chest X-ray, ECG and blood pressure were normal.

^{59}Fe injection and whole body counting

After an initial measurement in the whole body counter to obtain a background reading, each patient was given intravenously 37 kBq (1uCi) ^{59}Fe ferric citrate via and antecubital vein and then remeasured in the whole body counter. Sterile ^{59}Fe citrate (code IFS.2P, Amersham international plc) was diluted with isotonic saline at pH3 under sterile conditions and millipore filtered before injection. The actual amount injected was determined by weighing the syringe before and after administration. A period of 9 - 14 days then elapsed to allow equilibration of ^{59}Fe uptake into circulating

erythrocytes, after which a further whole body measurement was made and a blood sample was taken for estimation of radioactivity concentration. This procedure was repeated for in order to measure MBL over two cycles before and after RaFEA.

The same RF generating equipment probe and belt were used as in section 7.

Patient details

Patient Number	Patient Init's	Age	Height (cm)	Weight (kg)	Day of Cycle Rx'd	PreRx Days Bleed	PreRx Max.no pads
1	PM	49	156	58.4	11	10	>24
2	KW	41	150	48.9	13	11	24
3	BB	43	160	60.2	10	8	22
4	LW	46	158	68.0	14	12	>24
5	PS	40	156	51.5	7	6	16
6	TP	42	161	87.9	9	7	18
7	MM	39	153	61.1	12	10	>24
8	RS	45	151	70.9	10	8	12
9	PR	53	160	140.0	14	13	14
10	MB	51	158	69.4	10	7	20
11	RS	38	142	82.1	6	8	12
12	PQ	46	159	69.2	4	4	14
13	LF	41	161	73.0	9	7	20
14	FG	50	158	68.1.	18	11	16
15	RP	39	152	64.2	?	9	>24

All patients had undergone diagnostic hysteroscopy and diagnostic curettage with a normal result within the previous 9 months.

19 Patients were recruited, but 4 excluded. 1 patient developed an ovarian cyst prior to RaFEA and needed a laparotomy, hysterectomy was performed simultaneously. 3 other patients failed to either complete the blood loss studies protocol.

All patients were treated without difficulty as day cases, and made uneventful recoveries. FSH levels were within the premenopausal range (<30 IU/ml) in all patients at the beginning and end of the experimental period. All other haematological and biochemical indices were within normal limits and unchanged at one and six week follow up.

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Results

Pre-RaFEA MBL results

Patient Number	Patient Init's	Hb (g/dl)	Estimated Blood Loss (2 cycles) (ml)	Estimated Blood Loss Per Cycle (ml)
1	PM	8.4	600	300
2	KW	12.1	599	300
3	BB	11.2	403	201
4	LW	9.8	1330	665
5	PS	10.5	386	193
6	TP	12.3	152	76
7	MM	10.1	859	429
8	RS	12.7	436	218
9	PR	11.6	522	261
10	MB	11.9	380	190
11	RS	10.1	269	134
12	PQ	11.3	281	140
13	LF	12.0	577	288
14	FG	11.2	506	253
15	RP	12.1	97	49

Values given for estimated blood loss per period are considered accurate to +/- 50 ml, based on studies performed with older equipment, and on the results obtained from our own single polycythaemic patient (see appendix 4).

Pre-treatment blood losses were very variable with a range from 97 to 1330ml and a mean value of 493ml.

Correlation between subjective loss and measured MBL

There was a positive correlation between subjective estimation of severity of menorrhagia and objective MBL measurement. If a 'points system' is created, where the number of days of bleeding is multiplied by the maximum number of pads used per 24 hours (MB. changed because of saturation or near-saturation), then the two may be compared. Patients using over 24 pad per 24 hours are counted as using 30 pads per 24 hours.

Numbers a too small to examine the significance of any recorded parameter such as height, weight or age on severity of symptoms.

Patients were closely questioned to ensure that there
was no history of blood loss from some other route
(accident/laceration, rectal bleeding, haematuria,
blood donation). There were no positive findings.

Patient Number	Pre-Rx Days Bleed.	Pre-Rx Max. No. Pads/24hr	'Menorrhagia Score'	Measured Loss/Cycle x2 (ml)
1	10	>24 (30)	300	600
2	11	24	264	599
3	8	22	176	403
4	12	>24 (30)	360	1330
5	6	16	96	386
6	7	18	126	152
7	10	>24 (30)	300	859
8	8	12	96	436
9	13	14	182	522
10	7	20	140	380
11	8	12	96	269
12	4	14	56	281
13	7	20	140	577
14	11	16	176	506
15	9	>24 (30)	270	97

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There is a strong statistical correlation between subjective judgment of MBL and measured loss in this study of +0.79 (Spearmans rank correlation coefficient).

Post RaFEA MBL Results

Patient Number	Pre-Rx Loss/ 2 Cycles (ml)	Post-Rx Loss/ 2 Cycles (ml)	Clinical Outcome
1	600	266	sig.reduct.
2	599	190	sig.reduct.
3	403	93	sig.reduct.
4	1330	94	amen.
5	386	66	spotting
6	152	87	sig.reduct.
7	859	0	amen.
8	436	24	amen.
9	522	30	amen.
10	380	182	sig. reduct.
11	269	129	no better
12	281	0	amen.
13	577	135	sig.reduct.
14	506	184	sig.reduct.
15	97	83	no better

After treatment with RaFEA the mean blood loss in 15 patients was 104 ml with a range of from 0 - 266 ml (see figure 39). The mean reduction in blood loss over 2 cycles after treatment was 389 (SEM 79) ml (p<0.001),i.e. a mean reduction of 195 ml per cycle.

At follow up of 15 patients 4 to 12 months after treatment, 7/15 (47%) were amenorrhoeic, 6/15 (40%) had experience a significant reduction in flow and 2/15 (13%) had reported treatment failure. It is interesting that the patient with the lowest pre-treatment MBL of 97 ml per 2 cycles and a post treatment MBL of 83 ml was one of these.

All patients remained well at follow up at monthly intervals (to 12 months). Biochemical and haematological indices were unchanged and within the normal range (as in section 5). FSH levels at six weeks and three months were premenopausal (<30 IU/ml).

Discussion

Many attempts have been made in the past to measure MBL objectively in women complaining of heavy bleeding, almost universally with the conclusion that less than
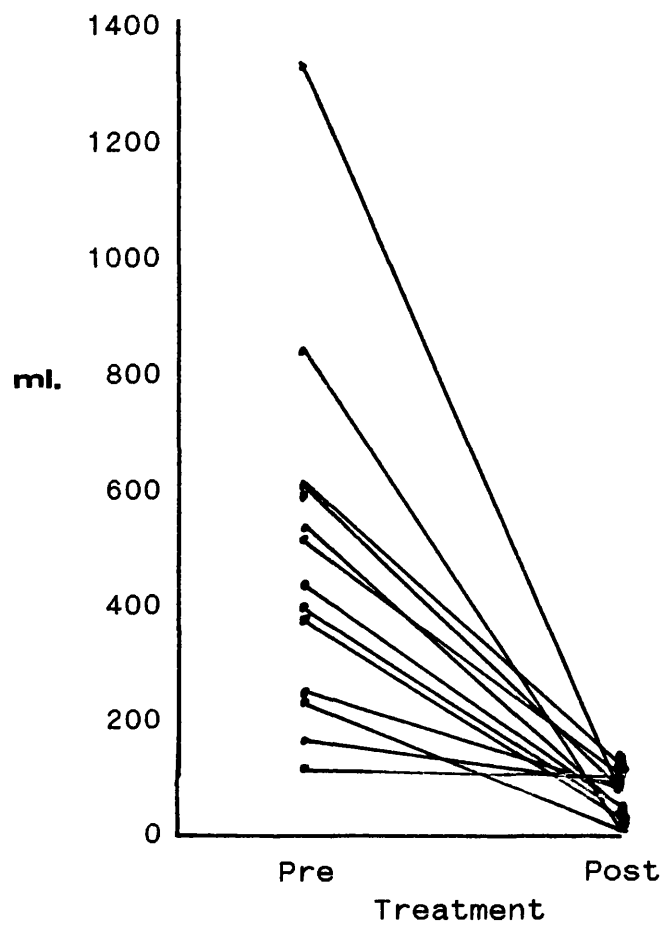
Figure 39 .   Effect of RaFEA On Measured Menstrual Blood
Loss

half are losing more than a normal amount (i.e. 80 ml per cycle). The majority of such studies have involved patients saving used sanitary pads for elution by alkaline extraction of haemoglobin (Haynes et al. 1977; Chimbira et al. 1980). However, different sanitary materials may not only retain different amounts of blood at saturation point (Grimes, 1979), but possess different affinities for blood, resulting in variable extraction efficiency during haemoglobin elution. Improvements in techniques may overcome this however, (Vasilenko et al. 1988; van Eijkeren et al. 1986). A further inaccuracy may arise due to micturition during menstruation. Corstens et al (1989) measured sanitary pad and urine radioactivity after labelling the blood with ^{59}Fe. They calculated that an average of 25% (range 1 - 69%) of MBL was lost during micturition and therefore not observed on pads. In addition, despite careful instruction, some blood may conceivably be lost at the time of pad change, especially if clots have formed within the vagina.

Conclusions

Objective study of MBL before and after RaFEA confirm

the previous clinical impression that the technique is
very effective in reducing MBL.

There is a case for considering the whole body counting
technique for measuring MBL in the assessment of new
treatments of DUB, because of greater accuracy compared
with the pad saving methods. The fact that patients
have to be exposed to radioactivity (albeit in very
small doses), high cost of radionuclides and the
scarceness of equipment does mean, however, that it is
unlikely to be used on a routine basis.

SECTION 9 - SUMMARY OF THESIS AND CONCLUSIONS

9.1.1. Feasibility

In vitro and in vivo studies have shown that it is possible to heat the majority or entirety of the endometrial cavity using radiofrequency electromagnetic energy, consistent with a histotoxic effect, safely, (ie. without significant unwanted heating of non-target tissues), provided safety precautions are rigorously followed.

9.1.2. Clinical Efficacy

Studies have suggested that approximately 80% of women treated will have a favourable therapeutic effect (either amenorrhoea or reduction in flow volume to acceptable levels).

Radioactive iron/whole body gamma counting studies performed before and after treatment confirmed the clinical impression that patients were achieving cures in the majority of cases.

9.1.3. Safety

The majority of patients develop varying degrees of lower abdominal pain and a watery bloodstained discharge which lasts 1-6 weeks after treatment. Infection of necrotic tissue does not appear to be a problem.

Two serious complications occurred due to technical failure. These patients were very obese (140kg, 120kg), and access to the cervix was problematic due to the intrusion of the anterior vaginal wall into the distended vagina, and an insulation fault in the prototype thermal probe. Owing to this, the anterior vaginal wall and bladder were accidentally heated, and vesico-vaginal fistulae resulted.

As a result of this, the specially designed vaginal guard was designed and built in order to protect the bladder, and no further problems occurred during the experimental time recorded in this thesis (see section 2 - Safety). At the time of writing, other centres participating in a multicentre trial have experienced two complications with burns (due to violations of safety protocol: inappropriate ECG equipment and

incompatible oximeter). A case of vesico-vaginal fistula has also been reported, due to inadequate insertion of the thermal guard. In fact, the surgeons inability to fully engage the guard into the fornices is recorded in the operating notes; unfortunately the treatment was proceeded with, in direct contravention of the safety protocol. Experience has shown that violations of safety protocol are the result of unfamiliarity with the details of such protocols on the part of medical or technical staff in theatre. Unyielding insistence that only staff who are totally familiar with all aspects of clinical RF use should enter theatre, especially if patient handling is involved, is of paramount importance.

9.1.4. Objective Demonstration of Tissue Effects

For reasons already alluded to, it proved impossible to obtain a hysterectomy specimen some time after RaFEA treatment. However, some patients consented to post-ablation hysteroscopy or Vabra aspiration.

Hysteroscopy demonstrated that the endometrial lining is converted into fibrous tissue, but intrauterine

synechiae formation does not appear to occur (in the small number of patients examined). This would, theoretically at least, reduce the risk of haematometra formation in those patients not rendered amenorrhoiec. Vabra aspiration repeatedly failed to obtain viable endometrial tissue from post-ablation patients (amenorrhoiec) in those subjects not willing to undergo post-treatment hysteroscopy (which was the majority).

9.2. Future Considerations

9.2.1. RF Endometrial Ablation (RaFEA) as an Accepted Technique

The major issue of safety has already been discussed, and it may be that the technique should be restricted to a specialist centre where full physics/engineering supervision is feasible (see section 2 - safety).

The potential advantages of RaFEA over hysterectomy, like other ablative techniques, are clear. The advantages over the Nd-YAG laser and hysteroresecto-scope are appreciable, but have yet to be proven by a large, comparative trial. Even if the results of RaFEA were no better than either, the advantages of operator

simplicity, speed of operation, lower cost of equipment (in the case of the laser system) have been clearly stated. Theoretically, provided the dangers associated with electric fields can be overcome, and provided the technique is applied correctly, RaFEA should be as safe, and possibly safer that the other methods, especially in view of fatalities experienced with transcervical resection of the endometrium.

9.2.2. Large Scale Trials

A large trial, possibly multi-centre, is essential in order to clearly determine whether or not RaFEA is effective, requiring several hundred patients. A strict protocol including rigorous entry criteria would be necessary, agreed upon by all concerned. Objective blood loss studies on such a large number of patients would probably be impractical, so that it would be important to devise a method of self-assessment of menstrual loss that would be as accurate as possible, and would mean that results from different centres are comparable.

It might be possible to design a smaller study, but

with statistically significant numbers of pre- and post-therapy cycles, where blood loss could be assessed objectively using a 'pad-save' and haemoglobin elution technique. We found that patients on the whole find this distasteful, and most were willing to take part in trials, provided they did NOT have to save used tampons or towels. Such a trial may well be very difficult to arrange, therefore.

The necessity of a randomised prospective trial versus hysterectomy has been pointed out by Stirrat (1990) and others.

The provision of detailed safety protocols and training of all staff involved at any centres participating is vitally important.

9.2.3. Treatment Technique

Treating patients post-menstrually, or giving pre-RaFEA danazol would mean that the basalis layer is maximally exposed to thermal damage, giving the best chance of a successful outcome. The latter is obviously undesirable in any trial situation because it would be difficult to differentiate between danazol and RaFEA

effect on blood loss. If the technique is used purely therapeutically, however, pre-RaFEA danazol may be effective. A further trial would be justified. Current work using a rotating probe with the tip slightly angulated in order to accommodate the proximal cavity is promising.

9.2.4. Duration of Therapeutic Effect

The permanence, or otherwise, of the therapeutic effect of RaFEA treatment requires evaluation by long-term follow up of patients. Patients from both pilot clinical trials recorded in this thesis are to be followed thus.

Data concerning the capacity of the endometrial basalis layer to regenerate are scant. It is known that the endometrium has a tremendous potential for regeneration, as demonstrated by the continuation of menstruation despite massive tissue insult inside the endometrial cavity from the multitude of physical and chemical agents that have been tried for endometrial ablation. However, it seems likely that once the basalis layer is destroyed, that area of the

endometrium becomes scarred and no longer capable of producing endometrium, as in Asherman's syndrome. This is not known for certain, however. It may be the case that the cells of the basalis layer are capable of growing laterally and 'patching' the damaged area. Long term follow up will answer this question. It is unclear whether possibly multi-potential cells in the stroma are capable of differentiating into 'true' endometrial components, but there is some evidence that myometrial smooth muscle may be newly formed from such cells (Fujii et al, 1989), and so the possibility exists.

Even if the effects of RaFEA were temporary, provided they lasted for a reasonable period of time, it might be feasible to offer patients RaFEA therapy at regular intervals, perhaps every 12-18 months, if they were keen to avoid hysterectomy. This would be particularly appropriate in the case of women approaching menopausal age (provided pathology is excluded) in order to 'tide them over' until menstruation ceased.

9.2.5. Risk of Endometrial Carcinoma

Although it may be that if the endometrium including the basalis layer is partially or completely destroyed after RaFEA the risk may be reduced, this cannot be assumed. A.Magos (1990, Personal communication) reports that islets of viable endometrial glandular cells exist within the stroma of the post-ablation 'endometrium'.

Some authorities feel that it may be the case that women who experience excessive menstrual bleeding are at increased risk of endometrial cancer, and this must be borne in mind at long-term follow up of patients treated with endometrial ablation by any technique.

Intermenstrual (in those patients not rendered amenorrhoiec) or irregular bleeding of any sort must be carefully watched for and investigated thoroughly as in any other patient by diagnostic hysteroscopy and curettage.

9.2.6. Long-Term Follow Up

RaFEA treated patients will be followed up in the long term, and carefully assessed for late complications including abnormal bleeding. There are no known long-

term effects of hyperthermia, as there are with radiotherapy for example, such as ischaemic fistulation.

Intrauterine synechiae have been demonstrated to occur with some forms of endometrial ablation, but this does not appear to be the case with RaFEA. Pyo- or haematometra formation therefore seem less likely, but still a possibility.

9.2.7. Treatment of Postmenopausal HRT Patients

The single advantage of achieving the age of menopause is the cessation of menstrual bleeding. The administration of hormone replacement therapy alleviates the unpleasant accompanying symptoms of the menopause, but in an intact woman reverses the single benefit nature confers upon the menopausal patient: 'periods' return. It is now widely accepted that un-hysterectomised women should be given cyclical combined preparations of oestrogen followed by 7-10 days of a progestogen to protect the endometrium from hyperplastic or neoplastic transformation. Many women experience a reversal of the feelings of well-being

gained from oestrogens during progestogen administration.

Women who have undergone hysterectomy are often treated with unopposed oestrogen, and therefore are not subjected to the unwanted effects of progestogens, although some authorities feel that there may be a beneficial 'protective' action on the breast in combined HRT treated women.

If postmenopausal women were treated with RaFEA prior to HRT, provided total endometrial ablation was achieved (ie. there was no bleeding after hormone challenge), then the reappearance of 'periods' would not be a problem. Those practitioners who feel that progestogens are best avoided if at all possible on the grounds of side effects would be able to give unopposed oestrogens without the problem of irregular vaginal bleeding, and perhaps a reduced or absent risk of endometrial carcinoma. This would require very careful study indeed, and it is highly questionable whether it is safe to regard an ablated endometrium in the same way one regards an absent one.

There would be considerable technical problems, however. The blood supply to the uterus is much reduced postmenopausally, and the massive cooling effect which helps prevent penetration of thermal energy beyond the inner uterus would be reduced. Extensive thermometry/dose studies would be needed.

9.2.8. Sterilisation

If the entirety of the endometrium is destroyed, the patient is presumably sterile. Whether or not this is actually the case, or whether ectopic pregnancy would be a problem, may only be speculated upon. In view of the ease and safety with which sterilisation may be carried out laparoscopically, it seems unlikely that TSEA for therapeutic sterilisation would be a viable proposition.

9.2.9. Final comment

Although endometrial ablation by any technique has received enthusiastic welcome (Townsend et al, 1990, MacDonald, 1990, Cheng, 1990), it is essential that a balanced opinion be maintained. In 1933 Lewis and

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Carroll reviewed the case of transurethral resection of the prostate (TURP) using the newly invented resectoscope at that time. Like most new techniques, the literature was replete with enthusiastic and encouraging reports at the time, hailing TURP as a 'minor procedure', destined to make prostatectomy 'obsolete' (Davis, 1931, Engel, 1932), with a mortality rate 'of nil' (Engel, 1932). In their paper entitled 'Prostatic resection - without the moonlight and roses', they detail 87 deaths and 168 major complications after TURP in approximately the first four years of the availability of the resectoscope. It is essential that we do not reach a time when it becomes necessary for such a paper to appear with regard to endometrial ablation by whatever method.

Only careful assessment and detailed trial will ensure that it does not.

The Luxtron Multichannel Electronic Thermometer

Luxtron Corporation Model 1000 Fluoro-optic eight channel thermometer, California, USA.

This device is capable of measuring temperatures very accurately, after calibration, in the range 0-70 degrees celsius with an accuracy of +/- 0.1 degree, from eight different probes simultaneously.

Calibration is effected by placing the temperature probes of the Luxtron unit in a water bath of known temperature (measured using a high-accuracy mercury thermometer, +/- 0.1 degrees), and running the unit through its calibration cycle. All readouts are then set to match the mercury thermometer.

The more commonly employed electronic devices for measuring temperature are of little use when heating is effected by high intensity RF electric fields. This is because self heating of thermistors or thermocouples occurs, leading to inaccuracies due to falsely high readings.

Using the Luxtron device, no such self heating occurs. Each probe consists of a fine plastic tube (approximately 22G) containing fibre optic bundles, at the sensor end of which is a crystal of magnesium fluorogermanate. This fluorescent substance emits light of a different wavelength to that incident upon it. The rate at which the energised crystal decays and subsequently emits light is analysed by a processor within the main unit. The rate of decay is directly proportional to temperature. At higher temperatures the emitted light is given off quickly, and the opposite is true at lower temperatures.

A pulse of light energy at 400nm from a xenon flash tube within the machine is transmitted along the probe tubing and is incident upon the fluorogermanate crystal at the end of the fibre optic line. The return pulse, at 600nm is then translated into temperature.

The disadvantage of the system is cost: approximately £22,000.

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APPENDIX 2 - Measurement Of RF Field Strengths In The Operating Theatre During RF Endometrial Ablation

Levels of RF in theatre were measured in order to ensure that RF endometrial ablation does not pose a significant environmental hazard to theatre staff.

On 7th December 1990, ERA Technology was commisioned to measure ambient RF levels using a Rohde and Schwartz ESH2 Receiver in conjunction with a small passive loop aerial and balun. The values recorded were within those recommended by the National Radiological Protection Board (NRPB).

A copy of their report is reproduced in the next few pages.

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EMC - COMMERCIAL AND INDUSTRIAL DEPARTMENT

MEASUREMENTS OF RF FIELD STRENGTHS DUE TO ROCKET MEDICAL MENOSTAL GENERATOR AND PROBE AT WATFORD GENERAL HOSPITAL

H R Mohammed

ERA Test Report 5043/11D5/1

Report approved by   :   *A J Maddocks*

A J Maddocks
Deputy Division Manager
EMC - Commercial & Industrial
Department

January 1991

HRM/JJ//G00010/11D5/1

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REPORT SUMMARY SHEET 1

ERA Test Report No:	5043/11D5/1
Survey of:	RF Field Strength
Purpose of Survey:	Safety Assessment of Menostal Generator and Probe
Address of Site:	Watford General Hospital Vicarage Road Watford WD1 8HE
Survey Requested By:	Rocket Medical Electronics Ltd 5 Lavant Street Petersfield Hampshire GU32 3EL
Order No:	Letter dated 28.11.90.
Site Liaison	H M Clarke
Test Specification(s):	HSE Guidance Note PM51 (Jan 1986)
Survey Started:	7 December 1990
Survey Completed:	7 December 1990
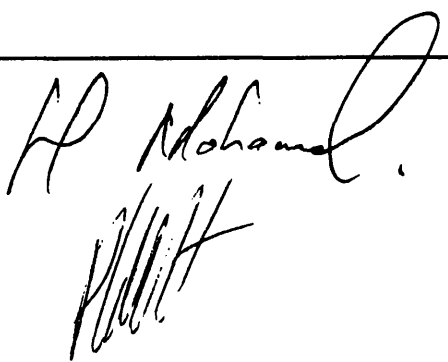
Test Engineer:	H R Mohammed	
Report Written By:	H R Mohammed	
Project Leader:	P C E Collett	
Client's Representative:	H M Clarke	

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MEASUREMENTS OF RF FIELD STRENGTH DUE TO ROCKET MEDICAL MENOSTAL GENERATOR AT WATFORD GENERAL HOSPITAL

1   INTRODUCTION

At the request of Rocket Medical Electronics Ltd ERA Technology Ltd has carried out a survey of the electromagnetic field strength of the Menostal generator and probe in the operating theatres at Watford General Hospital.

With industrial RF apparatus the main aim is to maximise the energy absorption within the material being processed. However there are likely to be some stray reactive and radiative fields from the apparatus. These stray fields, if not shielded or otherwise controlled at source are transmitted into the workplace, where they may be absorbed by the operator and other employees. The Health and Safety Executive Guidance Note PM51 deals with recommended safety limits for operation of plant and machinery and recommends fields strength levels which are safe enough for operators to operate the apparatus. High levels of rf field strength can also cause malfunction in other electronic equipment, and it is understood that some problems have been experienced in monitoring equipments used in association with the equipment under consideration.

The Menostal equipment is used for treatment on patients to burn out various tissues in the body. The equipment consists of a generator with a probe and belt. The probe is inserted into the patient and the belt wrapped around the patient. RF energy is then sent down the probe to burn the relevant tissues.

The Menostal operates at a frequency of 27.12MHz in two distinct phases.

Phase 1 : Calibration

During this phase the probe is placed within the patient and the probe/patient load is matched with the drive circuitry. This calibration phase takes place at about 20W at the operating frequency of 27.12 MHz.

Phase 2 : Treatment

During this phase power is sent to the probe for a period of about 15 minutes. The actual power applied will depend on probe size and patient type and is normally within the range 300-550W at 27.12MHz. Power is varied during the treatment in order to keep the tissue temperature around the optimum to obtain the correct treatment result.

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At the time of the survey the Menostal generator and probe was fully operational. The measured levels of field strength have been compared with the NRPB (National Radiological Protection Board) proposed limit quoted in Guidance Note PM51 (January 1986) from the Health and Safety Executive. The NRPB Proposals of 1982 indicate a limit of 0.184 amps/metre for an operating frequency of 27.12 MHz, the limit is given by 5.0/F amps/metre (where F = Frequency in MHz)

2   SUMMARY OF TESTS

2.1   Test Locations

Measurements of measured field intensity of the Menostal generator and probe were made at various locations as shown in Figure 1.

The measurements were made during the operating process of the Menostal generator and probe since this involved the higher power values which would result in higher field strengths.

2.2   Test Procedure

The magnetic field intensity was measured at a frequency of 27.12 MHz using a Rohde and Schwarz ESH2 Receiver in conjunction with a small passive loop aerial and balun. The measurements were made a distance of 0.3 metres from the generator and probe and at other positions as shown in Figure 1. Details of all the measuring equipment used are given in Appendix A of this report. The magnetic field intensity is quoted in terms of equivalent plane wave magnetic field intensity for comparison with the NRPB proposed limit for field strength.

3   RESULTS

The results of the measurements are presented in Tables 1 to 3 as follows:-

Table 1

Standard Feed Cable Configuration

Position	Magnetic Field Strength dB (μV/m)	dB(μA/m)	(A/m)	Proposed Limit (A/m)
1	145	93.5	0.050	0.184
2	143	91.5	0.037	0.184
3	123	71.5	3.76×10^{-3}	0.184
4	117	65.5	1.88×10^{-3}	0.184
5	117	65.5	1.88×10^{-3}	0.184
6	119	67.5	2.37×10^{-3}	0.184
7	113	61.5	1.18×10^{-3}	0.184
11	125	73.5	4.73×10^{-3}	0.184
12	97	45.5	1.88×10^{-4}	0.184
13	110	58.5	8.41×10^{-4}	0.184
15	107	55.5	5.96×10^{-4}	0.184
16	115	63.5	1.49×10^{-3}	0.184

Conditions at the time of measurements:

Patient: well built body

Power to Probe: 350W

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Table 2

Direct Feed Configuration

Position	Magnetic Field Strength dB (μV/m)	dB(μA/m)	(A/m)	Proposed Limit (A/m)
1	123	71.5	3.76×10^{-3}	0.184
2	137	85.5	0.0188	0.184
3	120	68.5	2.66×10^{-3}	0.184
4	129	77.5	7.49×10^{-3}	0.184
5	124	72.5	4.22×10^{-3}	0.184
6	115	63.5	1.49×10^{-3}	0.184
7	123	71.5	3.76×10^{-3}	0.184
8	111	59.5	9.44×10^{-4}	0.184
9	111	59.5	9.44×10^{-4}	0.184
10	127	75.5	5.96×10^{-3}	0.184
11	120	68.5	2.66×10^{-3}	0.184
12	113	61.5	1.19×10^{-3}	0.184
13	110	58.5	8.41×10^{-4}	0.184
14	125	73.5	4.73×10^{-3}	0.184
15	109	57.5	7.49×10^{-4}	0.184
16	119	67.5	2.37×10^{-3}	0.184
17	133	81.5	0.0118	0.184

Conditions at time of measurements:-

Patient   medium build body

Power to Probe: 300W

Table 3

Transmision Line Feed Configuration

Position	Magnetic Field Strength dB (μV/m)	dB(μA/m)	(A/m)	Proposed Limit (A/m)
1	129	77.5	7.49×10^{-3}	0.184
2	133	81.5	0.0118	0.184
7	105	53.5	4.73×10^{-4}	0.184
16	121	69.5	2.98×10^{-3}	0.184
17	131	79.5	9.44×10^{-3}	0.184
18	95	43.5	1.49×10^{-4}	0.184

Condition at time of measurements:-

Patient   Medium build body

Power to Probe: 300W

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Table 4

Position points relative to the Menostal generator and probe (Refer to Figure 1)

Position	Description
1	Above Probe
2	Below Probe
3	Left side of belt
4	Right side of belt
5	Top of patient's head
6	Below patient's head
7	Top of monitoring equipment table
8	Operator side of generator
9	Above generator
10	Generator mains cable
11	Front wall 2.9m away from patients head
12	1m away from (11)
13	1m away from (12)
14	Bottom of monitoring equipment table
15	Front wall, ground level
16	Top of belt
17	Probe cables
18	Back wall (4m away from probe)

4 CONCLUSIONS

The measured values of fields strengths from the Menostal generator and probe at Watford General Hospital were well below the HSE Guidance Note PM 51 limit of 0.184 amps/metre and therefore no hazard is identified.

Generally, well designed instruments should be immune to fields of up to 3V/m before any malfunctions may occur. The maximum field observed was at position 1 above the probe and the measured value was 145dB (μV/m), (17.8V/m). At the position of the monitoring instruments, fields of up to 2V/m were noted which could give rise to malfunctions in instruments which are not adequately immune. However no malfunctions on the monitoring instruments were observed during the measurement programme.

ERA
TECHNOLOGY
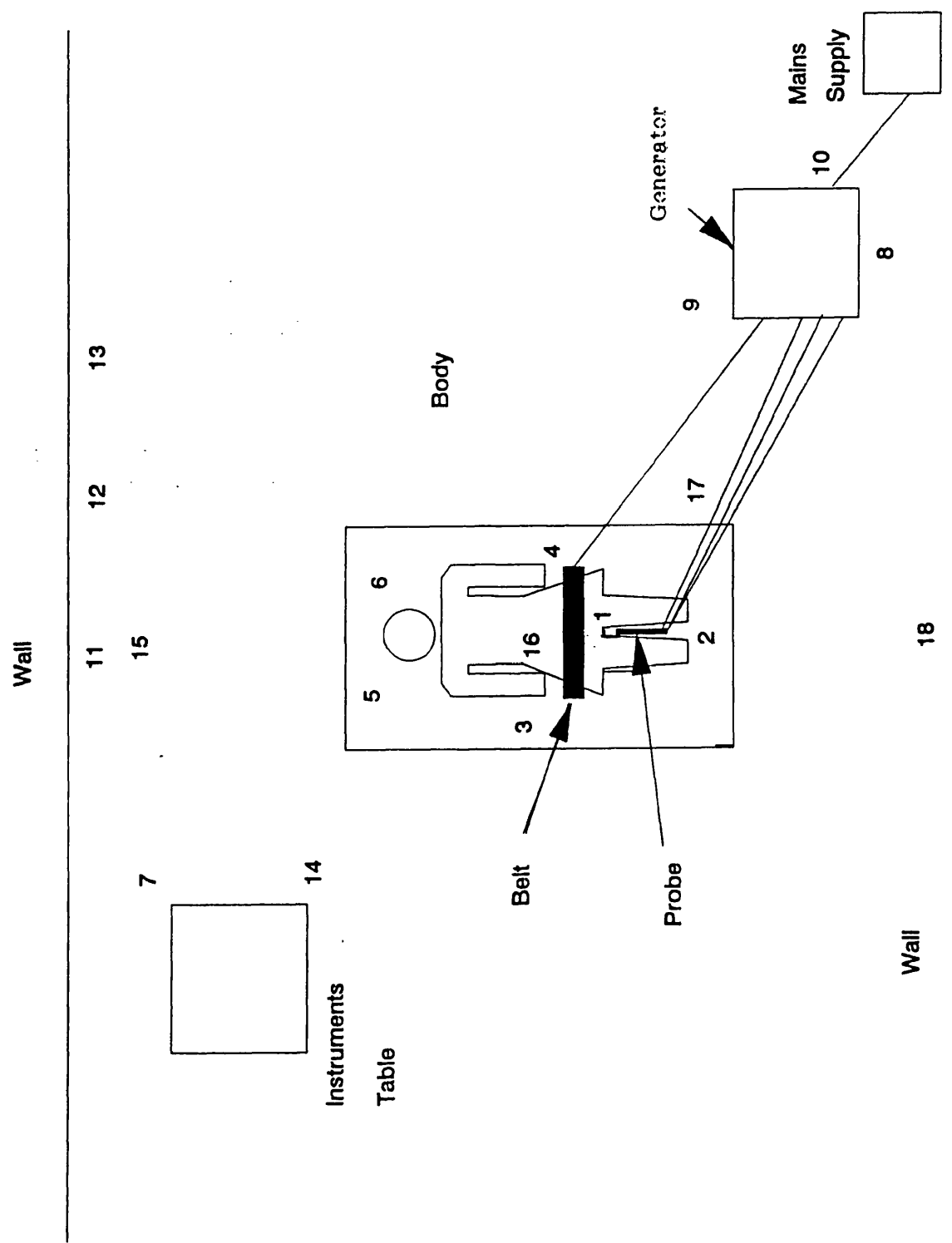
Figure 1: Position where measurements were made

Appendix A

Measuring Equipment

Equipment	Plant No	ERA Cal Due Date
Rohde and Schwarz ESH 2 Receiver	A701A	26/5/91
Loop Aerial 8 cm Loop	N/A	18/12/91
Balun Type XDLO4A	AZ002	19/10/91
10dB Attenuator	AZ121	5/4/91
10dB Attenuator	AZ147	16/12/90
10dB Attenuator	AZ116	28/2/91
MDS 20 Clamp	A309A	12/2/91

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APPENDIX 3 - Histochemical Technique For Demonstration

Of Presence Of Glucose-6-Phosphate-Dehydrogenase

The presence or absence of the intracellular enzyme glucose-6-phosphate-dehydrogenase (G6PDH) was used histochemically in section 4 (in vitro histochemical studies) to demonstrate the heating pattern achieved within the uterine cavity, and in section 6 (in vitro histochemical studies) to ensure that there were no areas of tissue subjected to excessive heating.

Although such histochemical techniques are useful for examining zones of tissue destruction after exposure to transient thermal insult (such as laser or diathermy), they are of limited value in assessing tissue destruction after exposure to hyperthermia. Hyperthermic tissue destruction relies upon the initial partial denaturation of cytoskeletal proteins, notably spectin (Hahn, 1987). Thus tissue which may be completely non-viable after hyperthermia treatment will still show active intracellular enzymes when examined histochemically, unless an intracellular temperature of 60 degrees or more has been achieved. The important difference between simple high temperature destruction

and hyperthermia is the element of time. Transient high temperature exposure (eg. the sweep of the laser or diathermy loop) results in brief periods of extremely high temperatures at the surface of the tissue (in the case of laser around 4,000 degrees), with a rapid fall off once the energy source has passed. Prolonged thermal penetration into deeper tissues, where temperatures have fallen off into the hyperthermic range (less than 60 degrees) does not occur to a significant degree. Hence, unlike the case with RF ablation, where exposure time is prolonged, hyperthermic tissue death is not a significant factor by comparison to the effects of simple thermal injury.

There are several enzymes suitable for demonstrating thermal tissue damage, such as nicotinamide adenosine dinucleotide H_2 diaphorase, or several in the dehydrogenase class. G6PDH was chosen because this technique was available at the time of experimentation.

The demonstration of dehydrogenases and diaphorases relies on the reduction of tetrazolium salts by hydrogen ions (released during oxidation) to produce formazans. Three tetrazolium salts are commonly used,

in this study nitro blue tetrazolium (NBT) was used.

NBT Stock Incubation Solution

NBT (4 mg/ml distilled water)	2.5 ml
Tris-HCL buffer, pH 7.4	2.5 ml
0.05 M Magnesium chloride	1.0 ml
Distilled water	5.5 ml

To 0.1 ml of this solution was added glucose-6-phosphate (disodium) 300 mg in 0.8 ml distilled water, and 2 mg of NADP.

Snap frozen sections were prepared on the cryostat, and incubated at 37 degrees for 45 minutes. Sections were then fixed in formal saline for 10-15 minutes, then washed in water. Sections were then counterstained with 2% methyl green (chloroform washed) and again rinsed. Glycerine jelly was used for mounting.

Slides were examined under the light microscope, and the green-appearing zones of enzyme deactivation measured using Vernier calipers. Areas of active enzyme appeared blue-purple (see experimental text).

(Bancroft and Hand, 1987).

Whole body counting provides an alternative method of estimating

blood loss to pad-saving studies which avoids some of the

potential errors inherent in the latter because the calculation is

based on differences between whole-body retentions and therefore

does not depend on the collection of radioactive (or haemoglobin)

losses from the body. In this technique, a quantity of

radioactive iron (^{59}Fe) is given intravenously and allowed to

bind to newly formed erythrocytes. With high incorporation of

tracer into circulating erythrocytes, iron loss from the body is

almost entirely due to blood loss, and a measured fall in ^{59}Fe

retention over a given time period (after allowing for radioactive

decay) reflects the amount of blood loss over the same period. If

the patients blood volume and/or ^{59}Fe concentration are known, the

fall in retention can be equated to the proportion of the total

blood volume that is lost (Warner, 1973; Price et al 1964; Holt et

al 1967).

METHOD

Ethical committee approval was obtained from Watford General

Hospital and Northwick Park Hospital Ethical Committees.

After an initial measurement in the whole-body counter to obtain a

background reading, each patient was given intravenously 37kBq

(1μCi) ^{57}Fe ferric citrate via an antecubital vein and then re-

measured in the whole-body counter. Sterile ^{59}citrate (Code

IFS.2P, Amersham International PLC) was acidified to pH 3 with

hydrochloric acid under sterile conditions and millipore filtered

before injection. The actual amount injected was determined by

weighing the syringe before and after administration. A period of

9-14 days then elapsed to allow equilibration of ^{59}Fe uptake into

circulating erythrocytes, after which a further whole-body

measurement was made and a blood sample was taken for estimation of radioactivity concentration. The initial injection and equilibrium measurements were arranged to occur respectively shortly after the end of a period and before the onset of the subsequent period. The equilibrium measurement was taken as the starting point for a measurement period extending over two menstrual cycles, after which further measurements of whole-body and blood radioactivity were made. The blood samples were lysed with solid saponin and aliquots (4ml) were counted in an automatic sample counter (Wallac Compugamma 1282). A counting sample for the blood samples was prepared by making up to 100ml a weighed aliquot of the same ^{59}Fe citrate solution used for the injection, and 4ml were counted. Whole-body counting was performed using a multi-detector system (eight NaI(Tl) crystals) in a 15cm thick steel sheilded cubicle (Smith et al 1979). Counts were obtained in the energy range 0.99 - 1.42 MeV to include both photopeaks of the ^{59}Fe gamma-ray spectrum. Whole body counting time was 400s, ensuring that errors due to counting statistics were less than 1%. On all counting occasions, care was taken to reproduce the position of the patient as accurately as possible to limit errors due to possible variations in counting geometry. Whole-body and blood radioactivity measurements were corrected for radioactive decay of ^{59}Fe, and blood loss calculated from the equation:

$$\text{Blood Loss (ml)} = \frac{2(\text{WB1} - \text{WB2})}{\text{B1} + \text{B2}}$$

where WB1 and WB2 are the whole-body retentions (% administered ^{59}Fe) at the start and end of the observation period respectively, and B1 and B2 are the measured concentrations of ^{59}Fe in blood samples (% administered ^{59}Fe per ml) withdrawn at the same times.

For patients who were re-examined sfter treatment, an initial

whole-body count was performed and a blood sample taken, to allow for correction for residual ^{59}Fe from the first injection. A second injection of 37kBq ^{59}Fe was then given and the same measurement procedure was repeated for two consecutive menstrual cycles, or where amenorrhoea was achieved, for a time period similar to that for the pre-treatment measurement. A four week interval between treatment and the second measurement was allowed to minimise errors arising from blood loss due to post-treatment sanguinous vaginal discharge.

The accuracy of the blood loss technique is largely determined by statistical errors on whole-body and blood sample counts, the effects of variations in counting geometry for whole-body counting, and errors in the preparation in samples including pipettings and weighings. Counting times were selected to ensure that counting statistical errors were less than 1% and the effect of variation in counting geometry was established by performing repeated whole-body measurements on each patient.

A direct estimate of the accuracy of the technique was obtained by performing the above procedure on a patient undergoing serial venesections for polycythaemia. On two separate occasions, 15 days apart, following administration of ^{59}Fe citrate, whole-body counts were obtained immediately before and after a known amount of blood was removed (approximately 1 unit, 500ml). The true volumes were calculated by weighing and measuring the density of the removed blood and these were compared with the blood losses estimated by whole-body counting.

Repeated whole-body measurements, requyiring repositioning of the patient, gave a mean paired difference of only 0.66 (SD 0.48)%

(n=18) of the mean whole-body count rate, showing that the

geometry error was minimised by careful positioning. Direct accuracy assessment of the technique using the polycythaemic patient showed excellent agreement: volumes of 470ml and 455ml of blood were actually removed, and were estimated to be 483ml and 461ml respectively.

In conclusion, the ^{59}Fe method of estimating blood loss is accurate and reliable provided volumes above approximately 200ml are measured. If volumes below 200ml are measured, the error of 1% of total body blood volume makes results less reliable, and calculated blood losses open to error.

Figure 40 shows the calendar for menstrual blood loss measurement.

Calender For Menstrual Blood Loss Measurement
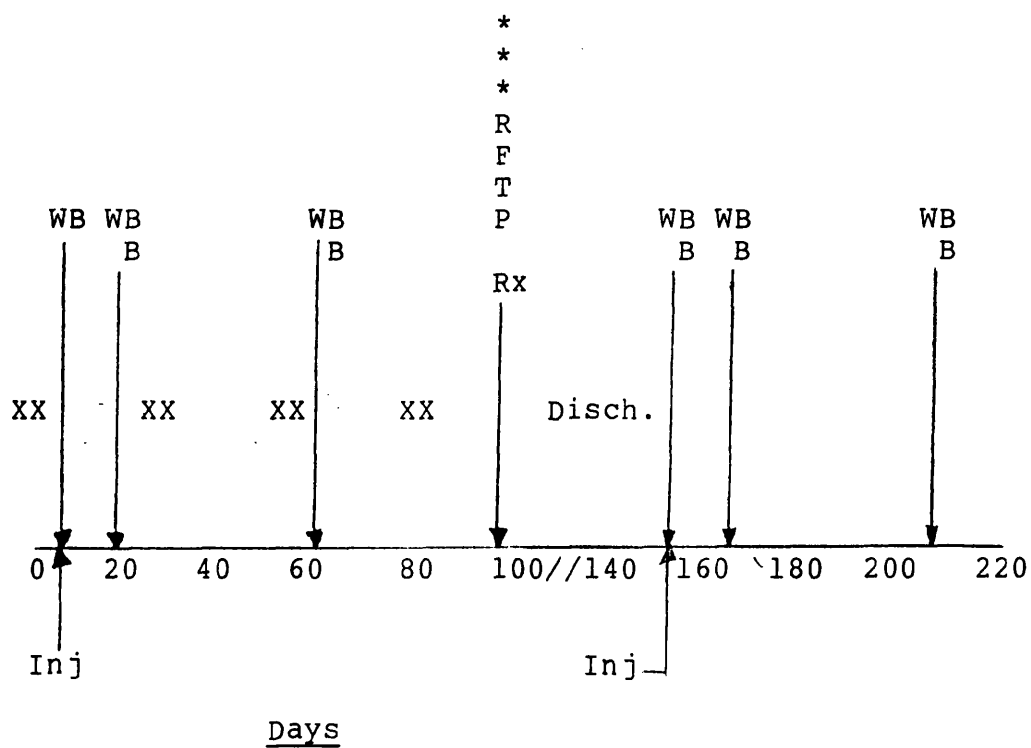
XX = menstrual period.

WB = whole body count

B = blood sample

Inj = injection 1μCi 59Fe ferrous citrate

***RFTP Rx = RFTP treatment

Disch. = Blood stained post-treatment vaginal discharge

Figure 40

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Abstract

Radiofrequency Induced Thermal Endometrial Ablation In the
Treatment Of Primary Menorrhagia: Invention And Primary
Assessment

Thesis For MD   J H Phipps   1990

The thesis is a record of the research and development of the
technique of Radiofrequency Induced Thermal Endometrial Ablation
(RITEA), based on an original concept of the author.

Many attempts have been made in the past to destroy the
endometrium in the treatment of excessive uterine bleeding where
organic disease has been excluded in order to avoid the
morbidity and mortality associated with hysterectomy. Until
recently, these have all been unsuccessful. In the last few
years, endometrial ablation has been successfully achieved using
two methods, both under direct hysteroscopic control: the
Neodynium-Yttrium-Aluminium-Garnet (Nd-YAG) laser, and the
electrodiathermy-driven hysteroresectoscope. Although both
these techniques yield good results, there are considerable
drawbacks. They are highly skilled, and the surgeon requires
much specialised practice before success may be expected.
Moreover, they are time consuming and said to be tedious. More
importantly, a continuous flow of a flushing medium through the
cavity is needed to maintain vision, and excessive absorption of
this may lead to serious morbidity, and occasionally mortality.
Penetration of the uterus and damage to pelvic/abdominal
structures has been reported.

RITEA is a technique which involves exposure of the endometrial
cavity to radiofrequency (RF) electromagnetic energy, which
causes very precise heating of the endometrium but not other
non-target tissues. This is achieved by means of a probe which
is placed within the cavity and energised for a particular
length of time. Target tissue is heated to around 53 degrees
celsius. Histotoxic effect relies upon the phenomenon of
hyperthermic tissue destruction, more usually used in cancer
treatment. Eighty percent of patients are cured, of which about
one third to one half are amenorrhoiec. The whole endometrium
is heated simultaneously because of the generation of an
electric field around the probe which does not rely upon direct
contact to heat tissue. The advantages of RITEA over the
hysteroscopic methods are possibly increased safety, greater
speed and therefore shorter anaesthetic, toxic
distension/flushing media are avoided, little skill is required,
and the equipment is likely to cost far less than an Nd-YAG
laser.

The thesis comprises sections on design and construction of the
RF thermal probe and associated equipment, in vitro studies in
fresh hysterectomy specimens, in vivo thermometry work, a
clinical trial of 30 patients for the purposes of ´dose ranging´
and finally a trial of 10 patients where efficacy is
demonstrated objectively by means of pre- and post-treatment
blood loss studies using radioactive iron and whole-body gamma
counting. Post-ablation hysteroscopic photographs are presented
which demonstrate the effects of RITEA on the endometrial
cavity.