attempted to view the urethral mucosa with a simple tube and candlelight. Hysteroscopy was the first gynecologic endoscopic procedure performed when Pantaleoni used a cystoscope to identify uterine polyps in 1869. Laparoscopy was first performed by Jacobaeus of Sweden in 1910, wherein a Nitze cystoscope, composed of a candle and a hollow tube, was used to illuminate the peritoneal cavity. Kalk of Germany was instrumental in developing laparoscopy into a diagnostic and surgical procedure in the early 1930s.[8]

Dr Kurt Semm (Fig. 1.5), a German gynecologist who specialised in infertility, was perhaps the most influential early advocate of modern operative laparoscopy[11]. In the 1960s and 1970s, Dr Semm invented the automatic insufflator, and hundreds of laparoscopic instruments, including a thermocoagulator, loop ligature and devices for extracorporeal and intracorporeal endoscopic knot tying. He was one of the first proponents of video monitoring for laparoscopy, using a series of lenses and mirrors in an articulated arm to connect the laparoscope to a ceiling-mounted video camera. He developed laparoscopic techniques for ovarian cystectomy, myomectomy, treatment of ectopic pregnancy, appendectomy and hysterectomy.

A hand-activated device for laparoscopic tissue removal was developed as early as 1973 and by 1993, the Steiner electromechanical morcellator was introduced.[12] The advent of electromechanical morcellation allowed for marked improvements in ease and speed of specimen retrieval with minimally invasive approaches.[13] As the field of minimally invasive gynecologic surgery has evolved to encompass increasingly challenging procedures, a number of power morcellation devices have been marketed to allow removal of large pathology via small incisions and avoid the morbidity associated with laparotomy.

Another technical innovation called myolysis has been described by Goldfarb and is based on earlier experience in Europe. Either neodymium-doped yttrium aluminum garnet (Nd:YAG) laser or bipolar needles are used laparoscopically to penetrate the myomata at multiple sites at a 90° angle to the uterus.[14]

Fig. 1.5: Kurt Semm

UAE for leiomyomas was first performed in the United States by Goodwin and colleagues in 1995.[15]

Sampson in 1913 was the first to study the blood supply of uterine leiomyomata and its effect on uterine bleeding.[16]

An unusual benign form of leiomyomata uteri, intravenous leiomyomatosis, was first recognized at the turn of the 20th century and has been reported sporadically since then. Before 1982, about 50 cases had been reported, according to Bahary and coworkers[17]. Marshall and Morris presented the first detailed report of this entity in the American literature in 1959. The characteristic feature of this peculiar smooth muscle tumour is the extension of the polypoid intravascular projections into the veins of the parametrium and broad ligaments.

In 1994, the first United States (US) Food and Drug Administration (FDA) approved robotic surgical device called AESOP (automatic endoscopic system for optimal positioning, computer motion, Inc.) was introduced. With this system, the surgeon can control the orientation of the laparoscope through voice commands[18]. In April 2005, the da Vinci Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA) was the first robot approved by the US FDA for gynecologic applications.[19] The da Vinci Robotic Surgical System (Intuitive Surgical) and Zeus Robotic Surgical System (Computer Motion) allow the surgeon to operate from a remote station with hand controls that can provide increased dexterity and minimize fatigue, tremors or incidental hand movement. These systems are being used in surgical centres, but have not gained universal adoption because of technical training and cost limitations. The optimal application for these devices is continuing to be defined.

Prior to the advent of modern minimally invasive surgery techniques, the primary surgical management of symptomatic leiomyomata for women desiring future fertility or uterine conservation was through laparotomy.

Recently, there is an increasing trend for minimal access surgery (MAS) for treatment of uterine myomas. Laparoscopic myomectomy has provided minimal invasive alternative to laparotomy for subserosal and intramural myomas. It is associated with faster postoperative recovery and potentially less postoperative adhesions. Main concerns are however subsequent fertility, reproductive outcome and long-term recurrence. Other alternatives are laparoscopic assisted myomectomy, laparoscopic ultraminilaparotomic embolised myomectomy, laparoscopically-assisted transvaginal myomectomy, myolysis and cryosurgery. Hysteroscopic access is required for submucous myomas.

other hand, significantly more PDGF receptor sites per cell are seen in leiomyomas than in the myometrium, although the PDGF receptor binding affinity in the tumour cells is lower than that of the myometrium. Perhaps the most interesting aspect of PDGF in leiomyomas, however, may not be its growth factor role, acting in isolation, but rather its action in conjunction with other growth factors such as EGF and IGFs.[3]

The IGF-I almost certainly plays an important role because of its potent mitogenic capacity and the overexpression of both the peptide and its receptor in leiomyomas. Growth factors may be the mediators or effectors of sex steroid upregulation, but a primary dysregulation of one or more growth factors must also be considered.[3]

The significance of prolactin production in leiomyomas is not yet well defined; however, interest in this hormone has been stimulated by the finding that prolactin acts as a mitogen for vascular smooth muscle.[79] However, in a recent study, treatment of leiomyoma and myometrial cell cultures with a prolactin-neutralizing antibody inhibited cell proliferation, leading to conclusion that prolactin may be an autocrine or paracrine growth factor for both leiomyoma and myometrial.[80] At this date, it would seem that the prolactin story is unfinished, evolving and of further study.

CONCLUSION

Uterine leiomyomas, or fibroids, represent a major public health problem. It becomes symptomatic in one-third of these women. Although the initiator or initiators of fibroids are unknown, several predisposing factors have been identified, including age (late reproductive years), African-American ethnicity, nulliparity, and obesity. Nonrandom cytogenetic abnormalities have been found in about 40% of tumours examined. Oestrogen and progesterone are recognized as promoters of tumour growth, and the potential role of environmental oestrogens has only recently been explored. Growth factors with mitogenic activity, such as transforming growth factor-β3, basic fibroblast growth factor, epidermal growth factor, and insulin-like growth factor-I, are elevated in fibroids and may be the effectors of oestrogen and progesterone promotion.

On the basis of our current state of knowledge, we can only speculate upon the initiators of this common condition. Future research efforts may provide a better understanding, however, of the causes and mechanisms of uterine fibroid tumourigenesis. Insights resulting from elucidation of the basic biology of these tumours might then be successfully translated into preventative strategies that will reduce the incidence and/or morbidity of this disease.

REFERENCES

1. Leppert PC, Catherino WH, Segars JH. A new hypothesis about the origin of uterine fibroids based on gene expression profiling with microarrays. Am J Obstet Gynecol 2006; 195: 415-420.
2. Laughlin SK, Schroeder JC, Baird DD. New directions in the epidemiology of uterine fibroids. Seminars in Reproductive Medicine. 2010;28(3):204-210.
3. Flake GP, Andersen J, Dixon D. Etiology and pathogenesis of uterine leiomyomas: a review. Environ Health Perspect. 2003;111:1037-54.
4. Cramer SF, Horiszny JA, Leppert P. Epidemiology of uterine leiomyomas. With an etiologic hypothesis. J Reprod Med. 1995;40:595-600.
5. Parazzini F, La Vecchia C, Negri E, et al. Epidemiologic characteristics of women with uterine fibroids: a case-control study. Obstet Gynecol. 1988;72:853-57.
6. Samadi AR, Lee NC, Flanders WD, et al. Risk factors for self-reported uterine fibroids: a case-control study. Am J Public Health. 1996;86:858-62.
7. Marshall LM, Spiegelman D, Goldman MB, et al. A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. Fertil Steril 1998a;70:432-39.
8. Marshall LM, Spiegelman D, Barbieri RL, et al. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstet Gynecol 1997;90:967-73.
9. Ross RK, Pike MC, Vessey MP, et al. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. Br Med J (Clin Res Ed). 1986;293:359-62.
10. Velebil P, Wingo PA, Xia Z, et al. Rate of hospitalization for gynecologic disorders among reproductive-age women in the United States. Obstet Gynecol. 1995;86:764-69.
11. Lumbiganon P, Rugpao S, Phandhu-fung S, et al. Protective effect of depot-medroxyprogesterone acetate on surgically treated uterine leiomyomas: a multicentre case-control study. Br J Obstet Gynaecol. 1996;103:909-14.
12. Parazzini F, Negri E, La Vecchia C, et al. Reproductive factors and risk of uterine fibroids. Epidemiology. 1996;7:440-42.
13. Marshall LM, Spiegelman D, Goldman MB, et al. A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. Fertil Steril. 1998;70:432-39.
14. Glass AR. Endocrine aspects of obesity. Med Clin North Am. 1989;73:139-60.
15. Schneider J, Bradlow HL, Strain G, et al. Effects of obesity on estradiol metabolism: decreased formation of nonuterotropic metabolites. J Clin Endocrinol Metab. 1983;56:973-78.
16. Chiaffarino F, Parazzini F, La Vecchia C, et al. Diet and uterine myomas. Obstet Gynecol. 1999;94:395-98.
17. Goldin BR, Adlercreutz H, Gorbach SL, et al. Estrogen excretion patterns and plasma levels in vegetarian and omnivorous women. N Engl J Med. 1982;307:1542-47.
18. Gorbach SL, Goldin BR. Diet and the excretion and enterohepatic cycling of estrogens. Prev Med. 1987;16:525-31.
19. Adlercreutz H, Fotsis T, Heikkinen R, et al. Excretion of the lignans enterolactone and enterodiol and of equol in omnivorous

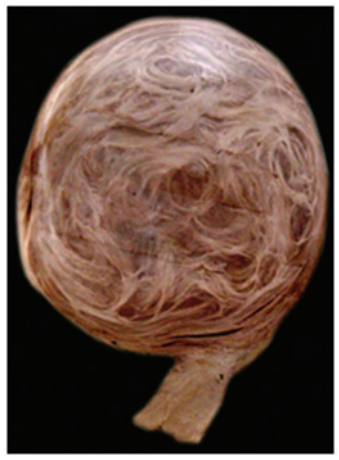

Fig. 3.6: Whorled appearance of fibroid cross section

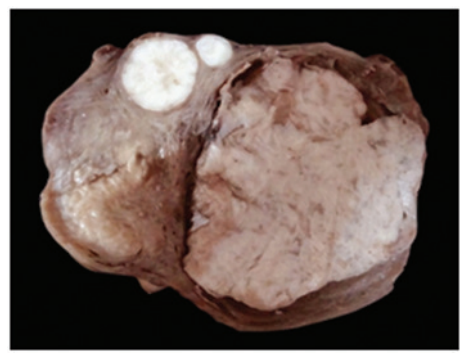

Fig. 3.7: Bulging of cut surface

of intratumoral pressure (Fig. 3.7). Large tumours may show yellow brown or red areas of softening.[1,6,9, 28–31]

MICROSCOPY

Microscopically, the tumour is composed of closely packed bundles of smooth muscle cells that resemble normal myometrial cells. The smooth muscle bundles are seen in different directions (whorled), and some bundles appear in transverse section (Fig. 3.8). These smooth muscle bundles are separated by vascular fibrous tissue. Individual tumour cells are elongated, spindle shaped, with a cigar-shaped (blunt ended) nucleus having finely dispersed chromatin and small nucleoli. They have abundant fibrillar eosinophilic cytoplasm and long, slender, bipolar cytoplasmic processes. These cells are uniform in size and shape, with scarce mitoses (Fig. 3.9). The stroma shows lymphocytes and plasma cells. The absence of coagulative necrosis, significant atypia or increased mitotic activity differentiate a leiomyoma from a leiomyosarcoma.[1,6,9,28-31]

High cellularity, prominent blood vessels, multinucleation and nuclear atypia with the appearance of prominent red or orange nucleoli having perinucleolar halos should alert the pathologist to investigate the possibility of the hereditary leiomyomatosis and renal cell cancer (Reed syndrome).[28,32]

Immunohistochemically, uterine leiomyomas characteristically express smooth muscle actin (SMA), muscle-specific actin, desmin, h-caldesmon, and vimentin.[28-30]

SECONDARY CHANGES IN A LEIOMYOMA

Secondary changes that may develop within a leiomyoma are as follows.[1,6,9, 28-31]

Hyaline Change

It may be localised or it may affect extensive areas of the tumour. Occasionally even the whole tumour may be hyalinised. The areas of hyaline change have a pale homogeneous eosinophilic, ground-glass appearance (Fig. 3.10).

Cystic Degeneration

It results from liquefaction of degenerated areas of the tumour. The cysts may contain gelatinous material.

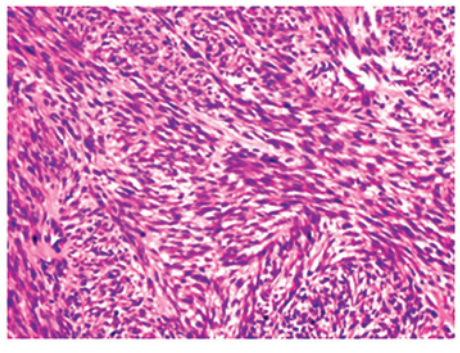

Fig. 3.8: whorled appearance of smooth muscle bundles

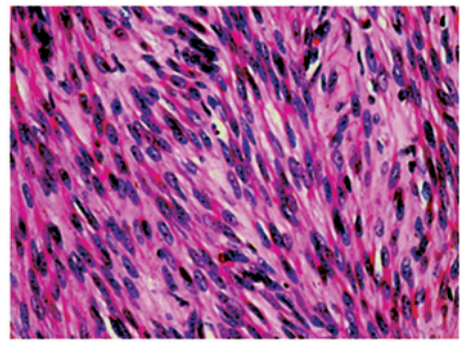

Fig. 3.9: Tumour cells with uniform size and shaper and scarce mitoses

LEIOMYOMAS ARE MONOCLONAL LESIONS

Chromosomal and molecular analyses have shown that development of each leiomyoma is an independent monoclonal process.[9] Analysis of multiple fibroids from the same patient revealed that each fibroid developed independently, as each one showed different chromosomal abnormality.[10,11]

If two fibroids (arising from the same uterus) showed similar chromosomal abnormality, they were either due to recurrent chromosomal aberration in the smooth muscle or just coincidental. Cytogenetically mosaic tumours were also reported to be clonal.[9]

This chromosomal heterogeneity, thus supports the multistep hypothesis of fibroid development, and also explains the clinicopathologic differences seen in fibroids, including variation in size or response to hormonal treatments.[12]

GENETICS OF FIBROIDS

Genetic liability of uterine leiomyomas has been evidenced by a variety of epidemiological, molecular and cytogenetic studies. Evidence for heritability of fibroids further comes from studies analysing ethnic predisposition,[13,14] twin studies,[15] familial aggregation,[16] as well as genetic linkage studies in families with uterine leiomyomata-associated heritable syndromes.

ETHNICITY

Black women are disproportionately affected by uterine fibroids—the incidence and prevalence rates being at least three times greater than those for white women even after other known risk factors are controlled.[13,14] Moreover, Black women are diagnosed more commonly with multiple fibroids, larger fibroids and at an earlier age.

FAMILIAL PREDISPOSITION

First-degree relatives of affected women have a fold higher risk of developing UL.[2,5] The concordance of fibroid diagnosis in monozygotic twins is almost twice that of dizygotic twins. Similarly, a study of a Finnish cohort found that monozygotic twins' concordance for being hospitalised for UL was twice that of dizygotic twins.[17]

SYNDROMES ASSOCIATED WITH FIBROIDS

Although benign, UL have been linked to malignancy through two genomic regions on chromosome1:

1. Hereditary leiomyomatosis and renal cell cancer (HLRCC): This autosomal dominant syndrome predisposes patients to benign leiomyomas of skin and uterus and early-onset renal cell carcinoma. The responsible gene was identified as fumarate hydratase (FH) that encodes a Kreb's cycle enzyme responsible for conversion of fumarate to malate.[18]

   The occurrence of leiomyomas as part of a heritable cancer syndrome is under appreciated and the finding of cutaneous leiomyomas (the mostcommon finding in HLRCC) warrants familial screening.[19]
2. Alport syndrome: It is a progressive nephropathy, the most common mode of inheritance being X-linked transmission. It is associated withuterine leiomyomas due to defect in COL4A5 and COL 4A6 genes.[20]

CYTOGENETIC STUDIES

Standard karyotyping detects chromosomal aberrations such as deletions, duplications and translocations, whereas comparative genome hybridisation detects deletions and amplifications. With further advancements in sequencing technology, small submicroscopic chromosomal abnormalities such as point mutations or epigenetic changes such as methylations have been diagnosed.[7,21,22]

The variety of chromosomal rearrangements, including but not limited to translocation, deletion and trisomy, predict different molecular genetic mechanisms for UL formation and growth.

CHROMOSOMAL ABERRATIONS

Although majority of leiomyomas (60%) are believed to be chromosomally stable, approximately 40% of leiomyomas have detectable cytogenetic rearrangements, such as deletions of 7q and rearrangements involving 12q15 or 6p21. The most common chromosomal aberration in leiomyoma, seen in approximately 20% of karyotypically abnormal leiomyomas, is the characteristic translocation, t(12;14) (q15;q24), specifically associated with leiomyoma.[23] An interstitial deletion of chromosome 7, del(7) (q22q32) is observed with a frequency of about 17% in karyotypically abnormal leiomyomas.

Leiomyomas with chromosome 7 deletions or translocations are usually found in the mosaic state with 46 XX cells. Rearrangements of 6p21 in leiomyoma occur with a frequency of 5% and include t(1;6)(q23;p21), t(6;14) (p21;q24), and t(6;10) (p21;q22), as well as inversions and translocations with other chromosomes.[3]

Other cytogenetic abnormalities of lower frequency include changes of the Xchromosome, including del(X)(p11.2), t(X;12)(p22.3;q15), -X, del(5)t(X;5)(p11;p15), del(X)(q12), del(X)t(X;3) (p22.3;q11.2) and inv(X)(p22q13).

In addition to chromosomal changes, point mutations in MED12 contribute to the development of leiomyomas. A study recently discovered mutations in MED12 exon 2 in 70% of 225 unselected uterine leiomyomas.[24]