Turner's Syndrome in Adulthood

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Turner's syndrome is the most common chromosomal abnormality in females, affecting 1:2,500 live female births. It is a result of absence of an X chromosome or the presence of a structurally abnormal X chromosome. Its most consistent clinical features are short stature and ovarian failure. However, it is becoming increasingly evident that adults with Turner's syndrome are also susceptible to a range of disorders, including osteoporosis, hypothyroidism, and renal and gastrointestinal disease. Women with Turner's syndrome have a reduced life expectancy, and recent evidence suggests that this is due to an increased risk of aortic dissection and ischemic heart disease. Up until recently, women with Turner's syndrome did not have access to focused health care, and thus quality of life was reduced in a significant number of women. All adults with Turner's syndrome should therefore be followed up by a multidisciplinary team to improve life expectancy and reduce morbidity. (Endocrine Reviews 23: 120–140, 2002)

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I. Introduction

TURNER'S SYNDROME (TS) IS the result of complete or partial X chromosome monosomy in a phenotypic female, associated with characteristic clinical features, the most consistent being short stature and gonadal dysgenesis.

Subjects with TS usually receive intensive medical care during childhood, but the majority are discharged from specialist clinics after the induction of puberty and attainment of final height. Until recently, adult women with TS had little access to focused health care, and, as a result, the medical profession has been slow to realize the extent of morbidity, particularly the extent of cardiovascular risk and the longterm consequences of estrogen deficiency. Affected women are susceptible to a number of medical problems, including cardiovascular disease, osteoporosis, and other endocrine, gastrointestinal, and renal disorders. Women with TS need long-term follow-up so that early medical intervention may reduce morbidity and improve life expectancy. This review highlights the medical disorders associated with TS and concentrates on the particular problems pertaining to adults with TS.

II. History

TS was first described in 1768 by the anatomist Giovanni Morgagni; he reported the postmortem findings of a short woman who showed renal malformations and gonadal dysgenesis. In 1902, Funke described a 15-yr-old girl with gonadal dysgenesis, short stature, absent puberty, congenital lymphedema, and a webbed neck (1). In 1930, Ullrich (2) gave the definitive description of the clinical features characteristic of TS, and the diagnosis was confirmed by karyotyping 57 yr later. However, the syndrome is named after Henry Turner (3), an American endocrinologist from Oklahoma, who in 1938 described seven women with characteristic phenotypic features of the syndrome. He emphasized the presence of gonadal dysgenesis and was the first to initiate estrogen replacement therapy.

Abbreviations: DM, Diabetes mellitus; GBY, gonadoblastoma locus on the Y chromosome; HRT, hormone replacement therapy; IBD, inflammatory bowel disease; MRI, magnetic resonance imaging; PHOG, pseudoautosomal homeobox-containing gene; SHOX, short stature homeobox-containing gene; TS, Turner's syndrome.

III. Epidemiology

TS is one of the most common chromosomal abnormalities, estimated to affect approximately 3% of all female fetuses. However, there appears to be a high fetal wastage with only 1% of these embryos surviving to term (4). Thus, TS is responsible for 7–10% of all spontaneous abortions. TS affects approximately 1 in 2,500 live female births (5, 6), corresponding to approximately 1.5 million women worldwide. Environmental risk factors for conceiving a child with TS are unknown. TS is not, in general, associated with advancing parental age (7).

TS is associated with a 3-fold increase in overall mortality and a life expectancy that is reduced by up to 13 yr (8, 9). Even after exclusion of deaths from congenital heart disease, the mortality rates remain excessive, particularly in women with 45,X monosomy. Cardiovascular disease is the most common cause of death in adults with TS (8, 9).

IV. Genetics

A. Cytogenetics

correlation with phenotype

TS is characterized cytogenetically by X chromosome monosomy, the presence of an abnormal X chromosome, or mosaicism of a 45X cell line with another cell line, which might be 46XX, 46XY or have an abnormal sex chromosome rearrangement. There is a correlation between the exact cytogenetic appearance and the phenotype in TS (Table 1). Pure 45,X monosomy is the most common karyotype and is associated with the most abnormal phenotype. In about two thirds of women with TS, the normal X chromosome is maternal in origin (4, 7, 10). Monosomy X results from nondisjunction as a result of failure of the sex chromatids to separate during meiosis in the parental gamete or in the early embryonic divisions. The latter usually results in mosaicism. Turner mosaics usually have a less severe phenotype and up to 40% enter puberty spontaneously before developing gonadal failure (11). Women with 45X/46,XY mosaicism have an increased risk of developing gonadoblastoma, and a minority of these women are masculinized. Structural X chromosome abnormalities are thought to occur as a result of breakages in the X chromosome with subsequent reunion of X chromosome sequences. Isochromosome Xq is the most common structural abnormality and is associated with autoimmune disorders and deafness, but congenital abnormalities are conspicuously absent (4). Women with the ring X chromosome are more likely to have psychological sequelae but are less likely to have structural congenital abnormalities, and spontaneous menses occur in about a third.

B. X inactivation and haploinsufficiency

In women with normal karyotype, early in embryogenesis, there is inactivation of one X chromosome in each cell. This is a random process, but faulty genes on the X chromosome are preferentially inactivated. An increasing number of genes, however, that escape inactivation and remain active on both X chromosomes have been identified (12–15). Some genes that escape X inactivation have homologs on the Y chromosome, so that their presence on both sex chromosomes is essential for normal development. The TS phenotype is considered to be the result of haploinsufficiency of genes that escape inactivation. Consistent with this notion is the finding that 31 of 34 genes that escape X inactivation map to the short arm of the X chromosome, deletion of which is known to account for most of the Turner phenotype (14).

C. Candidate "Turner genes"

Stature. Genes responsible for short stature have been localized to the distal part of short arm of the X (Xp11–22) and Y (Yp11) chromosomes, the pseudoautosomal regions that have been shown to escape X inactivation. Two groups of investigators simultaneously identified a strong candidate gene for short stature within pseudoautosomal regions that encodes for proteins found predominantly in bone fibroblasts (16-18). This gene, known as SHOX (short stature homeobox-containing gene), or PHOG (pseudoautosomal homeobox containing osteogenic gene), is expressed on both the inactive and active X and Y chromosomes. SHOX/PHOG point mutations have been shown to be associated with short stature (16, 17, 19). SHOX/PHOG mutations may also be responsible for some of the skeletal abnormalities associated with TS, such as the Madelung deformity of the wrist (18, 19). Clement-Jones and colleagues (18) showed that SHOX is strongly expressed during human embryonic limb development, which would be consistent with its role in the development of Madelung deformity and possibly cubitus valgus, high arched palate, and micrognathia. Interestingly, SHOX

common structural abnormality and is associated with autoimmune disorders and deafness, but congenital abnormal-TABLE 1. Cytogenetics of 196 women attending the Adult Turner clinics at the Middlesex and Oxford Radcliffe hospitals, UK, and

Karyotype	No.	%	Phenotype
45,X	95	48	Most severe phenotype. Highest incidence of structural cardiac and renal abnormalities.
46,Xi(Xq)	36	18	Structural abnormalities uncommon. Increased risk of autoimmunity, particularly thyroiditis and IBD, and deafness.
45,X/46,XX	21	11	Least severe phenotype. Increased mean height. Spontaneous puberty and menses in up to 40% .
46,Xr(X)	19	10	Spontaneous menses in 33%. Congenital abnormalities uncommon. Cognitive dysfunction in those with a small ring chromosome.
45,X/46,XY	11	6	Increased risk of gonadoblastoma.
45,X/46,X,idic(Y)	2	1	Increased risk of gonadoblastoma.
46,XXp-	3	1.5	Similar phenotype to 45,X monosomy.
46,XXq-	6	3	Variable phenotype.
other	3	1.5	

normalities similar to those found in TS (20). Additionally, nonspecific aneuploidy *per se* may contribute to short stature, as growth failure is seen in other syndromes associated with chromosomal imbalance (*e.g.*, Down's syndrome).

Ovarian function. Ovarian failure in TS could also be due to haploinsufficiency of a gene on the X chromosome that escapes inactivation. The regions of the X chromosome vital for normal ovarian development have been described as "critical regions" comprising the short arm distal to Xp11, Xq13-25, and Xq26-28 (21, 22). Several groups have sought genes disrupted at various X chromosome breakpoints, which could be candidates for ovarian determining genes (23–25). Other ovarian determining genes on the X chromosome have been identified as possible candidates because of the phenotypes described in knockout mice. For instance, the ZFX (zinc finger) gene on the distal Xp (15, 26), when ablated in mice, results in accelerated ovarian failure. A second candidate gene for gonadal failure in TS is the DFFRX (Drosophila fat facets related X), which maps to Xp11.4 (27). Certainly mutations of the Y homolog (DFFRY) have been associated with defective spermatogenesis (28). However, an alternative, and more likely, explanation for the cause of accelerated oocyte atresia in TS is that sex chromosome imbalance results in impaired meiosis and subsequent germ cell apoptosis (29, 30).

Lymphedema. Identification of genes responsible for other phenotypic features of TS has proven difficult, but several candidate genes on Xp are currently being investigated (21, 27, 30). A putative lymphedema gene that escapes X inactivation is thought to be located on the sex chromosomes, and haploinsufficiency of this may be responsible for lymphedema and the visceral abnormalities so common in TS. It is thought that this may lie on Xp; however, it has not yet been characterized.

Gonadoblastoma. Approximately 6% of women with TS have 45,X/46,XY mosaicism (31) and are at increased risk of developing a gonadoblastoma. This is a rare neoplasm that develops almost exclusively in the dysgenetic gonads of women with Y chromosome mosaicism. One or more genes on the Y chromosome, the GBY (gonadoblastoma locus on the Y chromosome) critical region, have been postulated to predispose dysgenetic gonads to develop gonadoblastoma. The GBY locus is thought to lie in a small region near the centromere of the Y chromosome, but its specific site remains elusive. A strong candidate gene is TSPY (testis-specific protein Y encoded) within the GBY locus (32). There has been recent interest in the significance of low-level Y mosaicism (mosaic level of <5%) and the risk of gonadoblastoma. Such mosaicism can be missed using conventional cytogenetic techniques, and some investigators therefore advocate routine screening for Y chromosome material using molecular genetic techniques such as PCR. However, in recent studies screening women with TS for low-level Y mosaicism, only 5% were found to have Y chromosome material that had not previously been picked up using conventional cytogenetic methods (33–35). Additionally, there have been no reported cases of gonadoblastoma developing in women with TS and low-level Y chromosome mosaicism (36). Thus, the routine screening for Y chromosome material by PCR is currently not recommended.

V. Clinical Features of Turner's Syndrome

There is a wide variation of clinical features seen in females with TS, ranging from the severe phenotype with short stature, gonadal dysgenesis, lymphedema, and characteristic dysmorphic features, to women with only a mild reduction in final height, or premature ovarian failure (Table 2).

A. Diagnosis

The diagnosis of TS may be delayed until adulthood in up to 10% of women. This is especially likely in females who enter puberty spontaneously and subsequently present with amenorrhea (primary or secondary) or infertility. The diagnosis is made on the basis of a chromosomal analysis. A peripheral lymphocyte karyotype is routinely analyzed and is diagnostic in the majority of cases. In rare instances, this karyotype is normal in females with TS mosaicism; however, if TS is suspected on clinical grounds, karyotyping of other tissue samples, such as skin fibroblasts, may be necessary (37).

B. Short stature

Short stature is an almost invariable finding in women with TS, present in all with monosomy X and in more than 96% of mosaic females or those with a structurally abnormal X chromosome. The mean final adult height is between 143 and 147 cm in untreated Caucasian females with TS (Fig. 1) (38–41).

The cause of growth failure in TS is currently unknown, but it is thought to be due to a primary bone defect. The genes responsible for growth, as previously stated (*Section IV.C*), are thought to lie in the pseudoautosomal region of Xp. There is no evidence that GH deficiency is a cause of short stature in TS although partial GH insensitivity may be a factor (42– 44). Treatment during childhood consists of early GH therapy in supraphysiological doses and estrogen replacement around the normal age of puberty. An average gain of 10 cm

TABLE	2.	TS:	clinical	features
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Feature	Frequency (%)
Short stature	98
Gonadal failure	95
Micrognathia	60
Cubitus valgus	47
Low posterior hairline	42
Short neck	40
High arched palate	38
Short fourth metacarpal	37
Multiple naevi	25
Webbed neck	25
Lymphedema of hands and feet	22
Nail dysplasia	13
Scoliosis	11
Madelung deformity	7

[Adapted with permission from B. Lippe: *Endocrinol Metab Clin* North Am 20:121–152, 1991 (5).]



FIG. 1. Distribution of height in 249 adults with TS attending the Turner clinic at the Middlesex Hospital, UK. Distribution of final height in women with Turner's syndrome (*bar chart*) and the UK population reference distribution (*solid line*). The majority of these women had not received GH therapy. It is hoped that with the early initiation of GH treatment in girls with TS, average final height will improve.

(range 3.9–24.8 cm) in final height may be achieved by the early introduction of growth-promoting therapies (45–51).

C. Bone abnormalities

Many of the physical stigmata of TS are a result of structural bone defects (5). Typically, females with TS have disproportionately short legs and an abnormal upper-to-lower segment ratio. This results in the appearance of a squarely shaped chest and widely spaced nipples. Cervical vertebral hypoplasia contributes to the short stature and also causes the short neck often seen in females with TS. Scoliosis may be present in approximately 10% of females, and it may or may not be associated with vertebral abnormalities.

Just under half of females with TS have cubitus valgus, or a wide carrying angle, as a result of a developmental defect of the head of the ulna. Similar abnormalities of the medial tibial and femoral condyles may also be present, resulting in a genu valgum. Short metacarpals and metatarsals are found in a proportion of women with TS, and a "bayonet deformity" (also known as Madelung deformity) of the wrists may be present as a result of lateral and dorsal bowing of the radius and subluxation of the distal ulna. These features may also be seen radiologically, in addition to crowding of the carpal bones and an osteoporotic appearance. Interestingly, the bone deformities do not cause disability in adults. In particular, an excess of osteoarthritis has not been reported in TS.

The characteristic facies of a female with TS is also primarily due to skeletal malformations. These result in micrognathia, a downward droop of the outer corner of the eyes and epicanthic folds, a high arched palate, and low-set ears.

A primary defect in bone formation is thought to exist in TS because of the numerous skeletal dysplasias associated with the syndrome in addition to short stature and a propensity for osteoporosis (see below). However, the molecular defect has not yet been characterized, although it has been hypothesized that deletion of a gene on the X chromosome may be responsible for such connective tissue abnormalities (18, 51).

D. Osteoporosis

Bone mass increases steadily during childhood and adolescence to peak in the second decade when it plateaus. Peak bone density attained is therefore an important determinant of ultimate skeletal health. There is a reduction in peak bone mass by 25% in women with TS (52, 53). There remains a great deal of speculation as to whether the reduction in bone mass seen in TS is a result of poor bone mineralization, and thus increases the risk of fractures, or is solely a consequence of delayed skeletal maturation and small bones. Ross and colleagues (54) noted a significantly decreased bone density in prepubertal girls with TS compared with chronological and bone age-matched controls. However, bone density in girls with TS is normal when compared with height-matched controls, suggesting that at least part of the reduction of bone mass is a result of delayed skeletal maturation. Significantly, however, the girls studied by Ross et al. (54) also had a fracture incidence that was 3 times that of normal controls. Furthermore, Shore and colleagues (52) showed that bone density remained low even after correction for height and skeletal maturation.

Adults with TS continue to show evidence of a reduced bone mass (55–57), and this has also been shown to be associated with an increased risk of fractures. Davies et al. (56) showed a fracture frequency of 45% in women with TS and of 33% in women with other causes of primary amenorrhea, both rates being far higher than the fracture rate seen in a control group. In contrast, Landin-Wilhelmsen and colleagues (58) found a lower 16% fracture prevalence in women with TS; however, this was still greater than the 5% prevalence in the control group. Gravholt and colleagues (59) have estimated that women with TS are 10 times more likely to develop osteoporosis and are twice as likely to sustain a fracture. In summary, although delayed skeletal maturation and small bones may result in an underestimation of bone mineral density, women with TS are at increased risk for fractures, and thus all efforts should be made to treat underlying osteopenia.

The effect of GH therapy on bone mass in girls with TS has been studied by several groups. GH treatment for at least 1 yr improves bone mineral density (58, 60, 61), although the bone mass remained below the normal value for age. Early estrogen therapy has also been shown to improve, but not normalize, bone density (52, 61). Mora and colleagues (62) found that girls who had started sex steroids before the age of 12 yr had a higher bone mass than those who started treatment after the age of 12 yr. The combination of estrogen replacement therapy and GH treatment results in a greater gain in bone mass (60, 63). In girls with TS who enter puberty spontaneously, bone mass has been found to be within normal limits (64).

After adolescence, estrogen replacement therapy seems to be the single most important factor in maintaining peak bone mass. Sylven and colleagues (57) looked at bone mineral density in 47 middle-aged women with TS and found that women with TS had a bone mass less than age-matched normal values. They also found that the duration of hormone replacement therapy (HRT) was the significant factor in maintaining bone mass. Stepan and co-workers (55) also demonstrated that women with TS have a lower bone mass compared with age and sex-matched normal values, but those women receiving HRT had a higher mean bone mineral density compared with those who were untreated (-2.3 sD)vs. -4.5 sp). Finally, Davies et al. (56) did not show a significant difference in bone mineral density or fracture risk in women with TS compared with women with other causes of primary amenorrhea, suggesting that estrogen deficiency is an important factor in the pathogenesis of osteopenia in TS.

Since bone mass is improved but not normalized after hormonal therapy (65), an intrinsic bone defect is likely. The cause of osteopenia in TS is probably a result of the combination of an intrinsic bone defect in addition to estrogen deficiency. However, if this were the case, one would expect bone density to be higher in women with a mosaic karyotype compared with 45,X monosomy, but there are no data correlating bone density in TS with karyotype (52, 53, 56, 65). Further research is required to determine whether loss of genes on the X chromosome may predispose women with TS to osteopenia. Additionally, further longitudinal studies are required to assess the prevalence of clinically significant osteoporosis and osteoporotic fractures in TS.

Estrogen replacement should be optimized and lifestyle advice given with regards to exercise and adequate calcium intake. Weight-bearing exercise has been shown to improve bone mass in women with TS (66). All women with TS should have a bone densitometry performed on transfer to an adult clinic, and bone mass should then be monitored, although the frequency of monitoring remains controversial. The role of bisphosphonates in the treatment of osteoporosis in women with TS has yet to be clarified.

E. Lymphedema

Lymphedema, the result of obstruction at the level of the lymphatojugular connection, is a major defect in TS, which is present in affected fetuses, particularly those with 45,X monosomy. When severe, this results in fetal wastage as a consequence of severe generalized lymphedema, but spontaneous resolution can occur with subsequent live birth. Milder lymphedema is responsible for some of the typical features of TS, such as a webbed neck, ptosis, and a low posterior hairline. Lymphedema of the hands and feet may be present at birth but often resolves. It may recur, particularly after the initiation of estrogen therapy. In most women, lymphedema may be controlled using support stockings and/or diuretics. Nail dysplasia (pitting nails and lateral hyperconvexity) pathognomonic of TS is also thought to be secondary to lymphedema. Fetal lymphedema may also be responsible for the development of aortic coarctation (see *Section VII.A*).

VI. Gonadal Function

In a karyotypically normal fetus, the number of germ cells rises progressively to 600,000 by 2 months post conception to a maximum of 7,000,000 at about 5 months gestation. The number of germ cells then decreases so that at full gestation only 50% of the germ cells remain. There is then a progressive germ cell degeneration up until the age of menopause (67).

The gonads in TS differentiate normally until the third month of gestation. After this period, the absence of part, or the whole, X chromosome in the germ cells results in an accelerated degeneration of oocytes and an increase in ovarian stromal fibrosis (68). Ovarian failure occurs within the first few months or years of life. Ultrasonic assessment of the pelvis in females with TS reveal the majority to have streak ovaries and, in many, the ovaries are too small to be identified (69). In a recent study of 93 females with TS, the ovaries were not identified in 44% of females (70). In females with TS who have not had estrogen treatment, the uterus is hypoplastic and remains prepubertal in size.

Most females with TS do not enter puberty spontaneously because of the early gonadal failure and subsequent estrogen deficiency. Spontaneous breast development is either minimal or does not occur, and primary amenorrhea is usual. However, this is not inevitable, as indicated by a recent study from Italy in which the incidence of spontaneous puberty in women with TS was found to be as high as 16% (11). The frequency was significantly higher in women with Turner mosaicism (40% *vs.* 9%). This is in keeping with our own observations in which the overall incidence of spontaneous menarche and puberty was 12%. Only 8% of those with 45,X karyotype and 10% of those with a structural X chromosome abnormality entered puberty spontaneously, as opposed to 47% of females with 45,X/46,XX mosaicism.

However, few women with TS will maintain ovarian function with resultant fertility. Spontaneous pregnancy occurs in less than 5% of women (11, 41), the majority occurring in those with mosaicism. Additionally, the outcome of these pregnancies is often poor (Table 3). Approximately 40% of conceptions end in spontaneous abortion or perinatal death. In the liveborns there is a 37% risk of chromosomal abnormalities, particularly Down's or Turner's syndrome, and congenital malformations, especially congenital heart and neural tube defects (71–73). However, it may be that these figures are affected by publication bias and that prospective monitoring of adult cohorts could reveal a more favorable spontaneous pregnancy outcome.

A. Sex hormone replacement therapy

The majority of women with TS require long-term estrogen replacement therapy. After the induction of puberty and the completion of growth, females with TS should be maintained on cyclical estrogen-progestagen therapy. Estrogen replacement therapy in adults with TS is important in the prevention of osteoporosis (57) and in reducing risk factors for atherosclerosis (106, 107). In addition, it has been shown recently that estrogen replacement may improve aspects of cognitive function in women with TS (108). The role of estrogens in the protection against colonic cancer remains tentative, but studies have shown that rates of colon cancer can be halved in postmenopausal women by estrogen replacement therapy (109, 110). This protection is extremely relevant in females with TS, as they have been shown to have an increased risk of colorectal neoplasms (59, 111).

The estrogen dose and route of administration should be individualized taking into account patient preference and coexisting illness (Table 4). The oral route is the most popular, but transdermal estrogen patches avoid first-pass hepatic metabolism and are therefore ideal in women with liver disease or hypertriglyceridemia. However, 10% of women develop skin reactions to transdermal preparations. Natural estrogen preparations such as conjugated estrogens or E2 valerate have a benefit over oral contraceptive preparations in that they nearly all offer continuous estrogen for 28 d without a pill-free week. A proportion of women with TS using the oral contraceptive will be symptomatic of estrogen in the pill-free week. In addition, the presence of ethinyl E2 in the oral contraceptive pill has been associated with an increased incidence of liver disease in women with normal karyotypes (112) as well as in women with TS (113). It may also have an adverse effect on lipid metabolism through its effect on hepatic metabolism, and it may exacerbate hypertension, a common problem in TS.

The progestagen should be given for a minimum of 10 d/month to prevent the development of endometrial carcinoma (Table 4). Alternatively, a continuous combined regimen, with the advantage of no menstrual bleeding after the first year of therapy, might be considered, although the long-term outcome of its use in young women is lacking. The risk of breast cancer in women with TS is not thought to be higher than in the general population (59, 111), and the use of

physiological doses of estrogens should not contribute to an excess risk. The duration of HRT after the age of 50 yr should be made on an individual basis, weighing the risks and benefits for each woman.

B. Options for fertility

Spontaneous pregnancies occur in less than 5% of women with TS and are associated with a high risk of fetal loss. Chromosomal and congenital abnormalities are present in almost half of surviving babies. Fertile women with TS should therefore be counseled with regard to these increased risks and be offered prenatal diagnostic testing. Moreover, they should be advised to consider the high risk of early ovarian failure when planning pregnancies.

The majority of women with TS, however, will be infertile. Pregnancy may be achieved by oocyte donation and in vitro fertilization. Oocyte donation has been available over the past 15 yr to treat women with premature ovarian failure of any cause (114). High-dose estrogens (E2 valerate, 4-8 mg/dby mouth) and progestagens (300-600 mg micronized progesterone transvaginally) are used to prepare the endometrium for implantation. Best results are achieved once the endometrial thickness is greater than 6.5 mm (115, 116). The pregnancy rate in women with TS who have had adequate endometrial preparation is approximately 40% per treatment cycle, a result similar to that achieved in other forms of ovarian failure (117, 118), with the highest results attained using fresh embryos. However, the risk of miscarriage in women with TS is high, with only 50% of pregnancies resulting in a live birth (116, 117). This is thought to be due to uterine hypoplasia in TS and possibly relative uterine ischemia during pregnancy (116). Most women with TS require cesarean section for delivery because of cephalopelvic disproportion resulting from their body habitus.

Women with TS who do become pregnant may be at increased risk from cardiovascular complications, particularly

TABLE 3		Spontaneous	pregnancy	in	TS
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Karyotype	${f Subjects}^a_{(n)}$	Pregnancies ^a (n)	Healthy pregnancies	Abortions or stillbirths ^a	Congenital or chromosomal abnormalities ^{a}
45,X	16	32	14	15	3
Mosaic	49	104	39	39	26
Ring chromosome	7	12	5	1	6
46,Xdel(Xp)	3	6	1	2	3
Total	80^b	167^{b}	$64~(38\%)^b$	$65~(40\%)^b$	38 (23%)

^{*a*} Data taken from the following references: Refs. 11, 41, 71–105.

^b Includes five in which details of karyotype were not given.

TABLE 4.	Suggested	HRT i	n women	with	TS
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Estrogen preparation	Dose	
Conjugated estrogens (oral) E2 valerate (oral) E2 transdermal patch	0.625–1.25 mg daily 2 mg daily 50–100 μ g/24 h. New patch twice	a week.
Progestagen	Cyclical dose (d 1–12)	Continuous daily dose
Medroxyprogesterone acetate Norethisterone	10 mg 0.7–1 mg	2.5-5 mg 0.35-1 mg

aortic root dissection (*Section VII.B*). At least three deaths have been reported in pregnant women with TS from aortic dissection (119, 120). All women should therefore undergo a full cardiological assessment before seeking to become pregnant, including echocardiography or magnetic resonance imaging (MRI) of the aortic root, cardiac valves, and left ventricular function. Hypertension is more common in young women with TS, and this should be monitored and treated aggressively. However, preeclampsia does not seem to occur with increased frequency in TS.

There is currently much research into the removal of functioning ovarian tissue followed by its cryopreservation with the aim of reimplantation at a later stage when fertility is required (121, 122). Its clinical application has centered mainly on women who are scheduled to begin cancer chemotherapy; however, it may also be suitable for the few women with TS who exhibit early evidence of ovarian function but are at high risk of later ovarian failure. Research into this technique is still in its infancy. There have been no cases to date of successful human ovarian autotransplantation. If this technique is considered, subjects and their families must be counseled about the uncertainty of future success rates associated with this ovarian cryopreservation. The optimum age for ovarian biopsy in females with TS with normal gonadotropins is unknown and should be individualized, possibly based on serum inihibin levels, a more sensitive indicator of ovarian function. However, it is likely that ovarian cryopreservation should be considered in childhood or early adolescence. Furthermore, because of the high risk of fetal abnormalities associated with spontaneous pregnancies in females with TS, donor oocyte donation may be more appropriate.

VII. Cardiovascular Disease

The increased mortality in TS is primarily a result of its cardiovascular complications (8, 9). It has long been known that left-sided congenital cardiac abnormalities are more prevalent in women with TS, but recently, other cardiovascular risk factors have come to light, particularly the increased risk of aortic dissection and ischemic heart disease.

A. Congenital heart disease

Congenital cardiac anomalies are common in females with TS, with a prevalence estimated to be between 23 and 40% (Table 5 and Refs. 123–125). These studies also indicate that

TABLE 5. Structural cardiac anomalies in TS

	No. (%) ^a
Total no. of patients assessed	1,126
Structural abnormalities	
Bicuspid aortic valve	132(12)
Coarctation of aorta	103 (9)
Aortic stenosis/regurgitation	38 (3.4)
Partial anomalous venous drainage of the	26 (2.3)
pulmonary veins	
Other	17(1.5)
Total	316 (28)

 a Data taken from the following references: Refs. 123, 124, 125, 131, 132, 134.

structural cardiac anomalies are most prevalent in women with pure 45,X monosomy and tend to be less common in those with an isochromosome Xq karyotype.

Bicuspid aortic valve is the most common congenital malformation affecting the heart (123–126). It is usually an isolated abnormality. However, it may occur in combination with other anomalies, particularly aortic coarctation, and, as it calcifies, may result in progressive valvular dysfunction, as evidenced by aortic stenosis or regurgitation. The cause of the abnormal aortic valve is unknown.

Coarctation of the aorta affects approximately 10% of women with TS and is an important cause of hypertension. It is particularly common in females with webbing of the neck (5, 127). This association, in addition to the high incidence of aortic coarctation in 45,X aborted fetuses with severe lymphedema (128), has led to the theory that aortic coarctation is a result of the abnormal lymphatic flow in TS altering intracardiac blood flow by compressing the ascending aorta (5, 127, 129). Aortic coarctation, providing it is the only cardiac abnormality, is usually surgically corrected in childhood with excellent results. Untreated, it may be complicated by aortic rupture, congestive cardiac failure, and persistent hypertension. Seirafi and colleagues (130), who studied the outcome of surgery in 176 patients with aortic coarctation, found that surgical repair before the first year of life was less likely to be associated with persistent hypertension (4.2% vs. 27%).

Other cardiac anomalies, such as partial anomalous venous drainage and mitral valve prolapse, are also more common in TS compared with the general population (131–133).

All left-sided cardiac anomalies associated with TS result in an increased susceptibility to infective endocarditis, and therefore prophylactic antibiotics before dental or surgical procedures are essential. Patients with cardiovascular anomalies require long-term cardiological follow-up.

B. Aortic dissection

In the last decade the association of aortic dissection and TS has been increasingly recognized (Table 6), with several

TABLE 6. Aortic dilatation and dissection in TS: a review of the literature

	No. (%)
Total no. of patients	70
No. of patients below 21 yr	33(47)
No. of patients above 21 yr	37(53)
45,X karyotype (data available for 44	36 (82)
cases)	
No. with structural cardiac abnormality	50 (71)
No. with hypertension	32 (46)
No. with no risk factor	6 (8.6)
No. presenting with aortic dissection	44 (63)
Site of aortic dilatation/dissection	
Ascending aorta	29 (49)
Descending aorta	9 (15)
Both	21(36)
Unspecified	11
Evidence of cystic medial necrosis	18(72)
(histology available for 25 patients)	
Deaths	25(36)

[Reproduced with permission from M. Elsheikh et al.: Clin Endocrinol (Oxf) 54:69-73, 2001 (134).] reports of sudden death. Aortic root dilatation is thought to occur with a prevalence estimated to be between 8 and 42% (134–137), although not every aortic root dilation necessarily goes on to dissect. In our series, 42% of adult women with TS attending a dedicated clinic had echocardiographic evidence of significant aortic root dilatation (134). Hypertension, an abnormal aortic valve, and other left-sided cardiac malformations have been shown to predispose to aortic dissection in Marfan's syndrome and the general population (138, 139), and in TS these risk factors are present in more than 90% of females who develop aortic dilatation (136). As with other structural cardiac anomalies, it is most commonly associated with 45,X karyotype.

Aortic dilatation or dissection may occur at any age, and in the published literature just under half the patients were diagnosed before the age of 21 yr (134). Aortic root dilatation is thought to be due to a mesenchymal defect (136), as pathological evidence of cystic medial necrosis has been found by several investigators. In the 25 case reports in which histological data were available, 71% had evidence of cystic medial necrosis. Additionally, there is evidence of other connective tissue abnormalities in TS, particularly in the skeletal system (140), and there are several features suggestive of a mesenchymal defect that are common to both TS and Marfan's syndrome. Additional research is needed to determine whether an abnormality of the X chromosome may affect collagen synthesis and be responsible for the connective tissue abnormalities seen in TS.

The influence of estrogens on the natural history of aortic dilatation is unknown. Aortic root dilatation often develops

before the administration of exogenous estrogens, and there have been no reports to suggest any deterioration after HRT. However, pregnancy certainly increases the risk of progression to aortic dissection (118, 119, 141), although this may be due to the increased hemodynamic load rather than the high estrogen state.

Echocardiography is the mainstay of diagnosis of aortic dilatation; however, studies have shown that magnetic resonance imaging (MRI) can detect dilatation missed on echocardiography (133). MRI should be used if aortic root dilatation is detected to examine the severity and provide more precise measurements relevant to follow-up. The current difficulty in the interpretation of images is the lack of normal values for aortic dimensions relevant to females with TS. The normal aortic root diameter correlates with height; therefore, use of the normal range for karyotypically normal women may produce falsely reassuring results. To obviate this problem, normal ranges based on age and body surface area should be used (142, 143). Alternatively, some investigators suggest using a ratio between the aortic root diameter and descending aorta (136). A ratio of greater than 1.5 is considered abnormal (Fig. 2). Prophylactic β -blockers or calcium antagonists have been used in Marfan's syndrome to halt the progression of aortic root dilatation with some success (144, 145). Their efficacy in females with TS has not been examined. It is essential, however, that hypertension is treated aggressively (134) and that elective surgical intervention should be considered for patients with critical or progressive dilatation. The natural history of aortic root dilatation remains unknown, but the risk of aortic dissection or rupture



FIG. 2. MRI of the aorta in a woman with TS showing a dilated aortic root highlighted with *paired arrows*. The ratio of diameter of the aortic root (a) to the descending aorta (b) is greater than 1.5.

may be as high as 60%; therefore, regular surveillance is recommended. Until more is known about the natural history of aortic root dilatation, it is currently recommended that females with normal echocardiograms are imaged every 5 yr and those with abnormal echocardiograms are followed up annually by a cardiologist (146).

C. Hypertension

The risk of hypertension is increased 3-fold in women with TS (59). It is estimated to occur in 7-17% of children and 24–40% of adults with TS (5, 41, 147). Furthermore, even girls with TS who are normotensive have been shown to have an abnormal circadian blood pressure rhythm, with loss of nocturnal reduction in blood pressure, increasing the risk of end-organ hypertensive damage (148, 149). Failure to recognize hypertension may contribute to the excess cardiovascular mortality in women with TS. In our clinic population, 24% (36/150) of women were hypertensive, and this was attributable to renal disease or aortic coarctation in only 20% (7/36). Thus, the majority of women have no obvious secondary cause for hypertension despite the young age of onset. Further studies are needed to determine the exact etiology of hypertension in Turner's patients without significant cardiac or renal disease. There does not appear to be an association with karyotype, and it is hypothesized that hypertension is secondary to small vessel renovascular disease (5), as elevated renin activity has been shown in hypertensive girls with TS before estrogen therapy is initiated (150). The use of ethinyl E2 as estrogen replacement therapy may exacerbate hypertension, but the use of natural estrogens and GH therapy does not seem to influence blood pressure (106, 107, 151).

D. Ischemic heart disease

The incidence of ischemic heart disease in adults with TS is unknown, but a recent epidemiological study from Denmark (59) indicates that women with TS may be twice as likely to develop coronary artery disease compared with the general population. Women with TS have several risk factors for ischemic heart disease and atherosclerosis that include, in addition to hypertension, insulin resistance and hyperlipidemia.

Insulin resistance. Type 2 diabetes mellitus (DM) is 2–4 times more common in women with TS compared with the general population (59, 152) and tends to develop at a younger age. Impaired glucose tolerance is even more prevalent, affecting 10–34% of females with TS (153–155). Karyotype does not seem to influence glucose tolerance. Cicognani *et al.* (153) have demonstrated impaired glucose tolerance in girls with TS as young as 5 yr old, well before the use of sex steroids or GH. Caprio and colleagues (156) have demonstrated an early metabolic defect in glucose uptake resulting in reduced insulin sensitivity and hyperinsulinemia, and this may explain the high incidence of carbohydrate intolerance in TS. They also showed that this was independent of body mass index, although obesity, a common problem in TS (155, 157–159), will aggravate the insulin resistance.

The cause of obesity in females with TS is unknown, but

may be related, in part, to estrogen deficiency. Certainly the introduction of HRT improves fat-free mass and waist-hip ratio in women with TS without affecting body mass index (106, 107). Gravholt and colleagues (106) also showed that women with TS had reduced physical fitness as evidenced by a reduction in maximal oxygen uptake, which is only partially improved by sex hormone replacement. Further research into the pathogenesis of obesity in females with TS is warranted.

Up to 50% of women with TS may be insulin resistant (5, 106). Hyperinsulinemia may be present in childhood, before hormone treatment. GH therapy has been shown to further aggravate hyperinsulinemia (157, 160, 161), but not glucose intolerance, as the effects are reversed 6-12 months after therapy is discontinued. The use of oxandrolone therapy in relatively high doses to increase final height may further exacerbate insulin resistance (162), resulting in glucose intolerance in 44% of oxandrolone-treated females with TS (147). Whether sex hormone replacement therapy aggravates glucose intolerance in women with TS remains unclear. Gravholt and colleagues (106) demonstrated a deterioration in glucose tolerance as assessed by an oral glucose tolerance test after 6 months of estrogen therapy, with an impaired insulin response. In contrast, we have demonstrated an improvement in insulin sensitivity in women with TS by the administration of HRT (107), which is consistent with several randomized studies in karyotypically normal postmenopausal women, showing a reduction in insulin levels with HRT (163, 164).

Gravholt and colleagues (59) also showed an 11-fold increase in the frequency of type 1 DM in their study population. This may, however, be due to misclassification of insulin requiring type 2 DM, as this has not been the experience of other groups (5, 41). Additionally, islet cell antibodies are not present to excess in females with TS (165, 166).

Hyperlipidemia. Hypercholesterolemia has been demonstrated in Turner girls as young as 11 yr and does not seem to be influenced by karyotype. Ross and colleagues (158) studied 137 girls with TS, all under 14 yr of age, and showed that girls above the age of 11 yr had significantly higher total, highdensity lipoprotein, and low-density lipoprotein cholesterols compared with karyotypically normal controls, irrespective of body mass index. A recent study of 28 women with TS (167) reported that up to 50% of women, median age 21 yr, may have hypercholesterolemia. However, other investigators have not confirmed that cholesterol values differ from those of karyotypically normal women (106, 161, 168, 169). Hypertriglyceridemia occurs with increased frequency in TS and may be a direct consequence of obesity and hyperinsulinemia (159).

GH therapy has been shown to reduce total and lowdensity lipoprotein cholesterol and increase high-density lipoprotein cholesterol in adolescent girls with TS (161), although it is unlikely that this effect is sustained once treatment is discontinued. Short-term studies looking at the effect of estrogen replacement therapy on metabolic parameters in TS have failed to show an effect on lipids (106, 107, 170). HRT has been shown to have a favorable effect on cholesterol concentrations in postmenopausal women (163, 171), and it may be that longer term trials are required to definitively assess the effect of HRT on lipids in females with TS.

Estrogen deficiency. Premature ovarian failure, as discussed earlier, is present in more than 90% of patients and results in the loss of the cardioprotective effect of estrogens seen in premenopausal women. Premature ovarian failure of any cause has been demonstrated to increase cardiovascular mortality (172), and the use of HRT in postmenopausal women is likely to reduce the risk of ischemic heart disease (163, 173). However, up to 24% of adult women with TS do not maintain estrogen replacement therapy after induction of puberty (174).

Women with TS should therefore have an annual cardiovascular evaluation. Endocarditis prophylaxis should be given to those with known cardiac anomalies. All adults with TS should have at least annual blood pressure measurements. Hypertension should be treated aggressively with an aim to keep the blood pressure below 140/80. There are no comparative trials published assessing antihypertensive agents in TS, but β -blockers and diuretics are currently the antihypertensives of choice as vasodilators may exacerbate ankle edema. However, more than one drug may be required to control blood pressure.

Women with TS should have an annual fasting blood glucose and lipid profile, and weight loss in obese patients should be encouraged. The effect of aggressive lipid lowering on the risk of ischemic heart disease in women with TS has not been studied. Estrogen replacement should be individualized.

Those women with no cardiovascular anomalies diagnosed in childhood should be echoed regularly to monitor aortic root diameter. It is still unclear as to how often this should be done, but the current recommendation is every 5 yr. If there is any doubt, MRI may be a useful adjunct in assessing aortic dilatation. Those women with a known cardiovascular anomaly should be followed up by a cardiologist.

VIII. Hypothyroidism

Radetti *et al.* (175) studied 478 females with TS, mean age of 15.5 yr, and found that 22.2% had positive thyroid autoantibodies, of which 27% (29/106) were hypothyroid and 3% were thyrotoxic. The incidence of autoimmune thyroid disease in females with TS increases with age. Chiovato and colleagues (176) demonstrated a doubling in the prevalence of autoimmune thyroid disease from the first to the third decade of life. There does not seem to be an increased frequency of positive thyroid autoantibodies or of hypothyroidism before the age of 10 yr (177–179). Germain and Plotnick (177) demonstrated a peak incidence of thyroid dysfunction at the age of 15 yr and that the ability of positive thyroid autoantibodies to predict the development of thyroid dysfunction increases from the age of 13 yr. Twenty-five to 30% of adults with TS are hypothyroid (41, 168) compared with 1.5% of adult women in the general population (180). Up to 50% have positive thyroid autoantibodies (155, 169, 181). In our series, approximately 41% of women had positive antimicrosomal and/or antithyroglobulin antibodies, but only 16% were hypothyroid (182). The incidence of Graves' disease is not increased in TS. This is perhaps surprising considering the similar pathogenetic mechanisms of autoimmune hypo- and hyperthyroidism.

Autoimmune thyroid disease has been found to be particularly prevalent in women with the isochromosome [46,Xi(Xq)] karyotype compared with other karyotypes (179, 183). Our series confirms this with 83% of females with 46,Xi(Xq), with or without mosaicism, having positive thyroid autoantibodies compared with 41% of 45,X females and 14% of females with other karyotypes (182) (Table 7). Other autoimmune diseases are also associated with the isochromosome X, suggesting that an abnormality of the X chromosome may be linked with autoimmunity. The exact pathogenesis of thyroid and other autoimmune diseases in TS is unknown.

The effect of GH therapy on the occurrence of positive thyroid autoantibodies has been studied by two groups with conflicting results. Nienhuis and associates (184) suggested that GH therapy increased the risk of developing thyroid autoantibodies but not the risk of developing clinical disease. However, this has been refuted by Ivarsson and colleagues (181), who found an increased prevalence of thyroid autoimmunity in 89 girls with TS compared with controls, but the prevalence did not rise after up to 5 yr of GH therapy. It may be that the rise seen in thyroid autoantibodies in the first study was related to the increase in autoimmune thyroid disease with age, but further data are required.

We suggest that all females with TS should have thyroid autoantibodies and TSH checked annually beginning at the age of 10 yr. If the thyroid autoantibodies become positive, then repeat measurements are not required and the patient should be followed up with an annual TSH measurement. Hypothyroidism should be treated promptly to avoid associated morbidity, particularly obesity and hypercholesterolemia.

IX. Renal Disorders

Congenital renal anomalies are approximately 9 times more common in females with TS compared with the general population (59). Lippe and colleagues (185) evaluated 141 unselected girls with TS by either an iv pyelogram or ultrasound and found that 47 girls (33%) had evidence of a structural renal malformation. Of 113 adults with TS attending

TABLE 7. The prevalence of autoimmune thyroiditis in 145 females with TS

	45,X	X isochromosome	Other karyotypes	Total	P value
No. positive thyroid autoantibodies (%)	35/86 (41)	20/24 (83)	5/35 (14)	60 (41)	${<}0.001 \\ 0.0034$
No. autoimmune thyroid disease (%)	12/86 (14)	9/24 (37.5)	2/35 (6)	23 (16)	

[Reproduced with permission from M. Elsheikh et al.: Clin Endocrinol (Oxf) 55:223–226, 2001 (182).]

another Turner clinic, 49 subjects (43%) had a congenital renal anomaly (41). Reports in the literature give a prevalence of structural renal abnormalities in TS between 25% and 43% (186-188). Renal abnormalities (Table 8) occur through a number of mechanisms: an early defect in ureteric budding may give rise to a double collecting system or absent kidney, and an abnormality in migration of the kidney from the pelvis may result in a pelvic or a horseshoe kidney. These abnormalities do not usually result in significant morbidity. However, the risk of pyelonephritis and pelvoureteric obstruction is increased, thus increasing the risk of chronic renal impairment. Surgical intervention was required in 4 of the 49 girls (8.5%) with renal tract abnormalities studied by Lippe and colleagues and in 8 of the 49 patients (16%) followed up by Sybert (41). The frequency of renal malformations is higher in females with 45,X monosomy but the association is weak and renal disease may occur with any karyotype (185, 188).

Renovascular abnormalities are also more prevalent in TS and may be at least partially responsible for the increased incidence of hypertension in TS.

All females with TS should therefore have a renal ultrasound performed at the time of diagnosis. If significant abnormalities are detected, appropriate evaluation and therapy should be instituted. Urinary tract infections should be treated vigorously and renal obstruction relieved. Subsequent monitoring for progressive renal impairment, either as a consequence of obstructive uropathy or recurrent infections, and hypertension is essential.

X. Gastrointestinal Disease

A. Inflammatory bowel disease

TS is associated with a greatly increased risk of developing ulcerative colitis and Crohn's disease (Table 9). The prevalence of inflammatory bowel disease (IBD) in the general population is estimated at 150–250 per 100,000 population, ulcerative colitis being twice as common as Crohn's disease (189). Gravholt and colleagues (59) calculated a 2-fold increase in risk of developing IBD in women with TS. However, other studies found the risk to be even greater. In one study, the IBD in TS was estimated at 3% (190). We looked at the prevalence of IBD in 270 women with TS whose medical details are held on the adult Turner register database and found a similar prevalence of IBD of 2.6%. In contrast to the general population, Crohn's disease in TS, which usually involves the colon, appears to be at least twice as common as ulcerative colitis. The reason for this is unclear. Gastro-

TABLE 8. Renal abnormalities in T	'S
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Abnormality	Incidence in TS
Double collecting system	5-11%
Horseshoe kidney	10 - 16%
Rotational abnormalities	6-8%
Ectopic kidney (including pelvic kidney)	2.5 - 3.5%
Absent kidney	2-5%
Ureteropelvic obstruction	3-5%
Aberrant blood supply	2%

[Adapted from Refs. 185, 187, 188.]

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TABLE 9. IBD in T

Diagnosis	Karyotype	Age of onset of IBD $\left(yr\right)$
UC	45,X/46,Xi(Xq)	40^a
UC	46,Xi(Xq)	16
UC	46,Xi(Xq)	31
UC	46,Xdel(Xp)	16
UC	46,Xdel(Xp)	20
UC	45,X/46,XX	13
CD	45,X/46Xi(Xq)	17
CD	45,X/46Xi(Xq)	28^a
CD	45,X/46Xi(Xq)	16^a
CD	45,X/46Xi(Xq)	21
CD	46,Xi(Xq)	13
CD	46,Xi(Xq)	15
CD	45,X/46,Xi(Xq)/47,Xi(Xq),i(Xq)	9
CD	46,Xi(Xq)	24
CD	46,Xi(Xq)	10
CD	45,X/46,Xi(Xq)	13
CD	45,X	18
CD	45,X	17
CD	45,X	40
CD	45,X	14
CD	45,X	15
CD	45,X	14
CD	45,X/46,XX	15
CD	45,X/46,Xr(X)	22
CD	45,X/46,XY	29

^{*a*} Death from IBD. CD, Crohn's disease; UC, ulcerative colitis. [Data taken from the following references: Refs. 190–200, in addition to own series.]

intestinal symptoms often develop at a young age, the median age of onset being 16 yr (range 9–40 yr). Inflammatory bowel disease is often severe in women with TS and has been fatal in at least three cases. Colectomy has been necessary in 40% of the reported cases, and complications such as fistula formation and sepsis are common.

Women with the isochromosome Xq karyotype are particularly susceptible, accounting for 52% of the reported cases of IBD in women with TS. The causes of Crohn's disease and ulcerative colitis are not known, but immunological dysfunction is thought to play an important role. IBD, like most immune-mediated diseases, is more common in women. Additionally, the increased risk of IBD in TS, particularly in the presence of an X isochromosome, would suggest that perhaps a gene on the long arm of the X chromosome (Xq) may be associated with immune dysfunction.

Ulcerative colitis and Crohn's disease should be ruled out in women with TS and unexplained diarrhea or gastrointestinal bleeding. Additionally, TS should be considered in adolescents with IBD and growth failure.

There have been several reports suggesting that women with TS are also at increased risk of gastrointestinal bleeding from intestinal telangiectasia (5, 201, 202). This is thought to be a developmental defect, but does not seem to be associated with vascular malformations elsewhere. An iron deficiency anemia is a common presentation, in addition to intermittent gastrointestinal hemorrhage. Fortunately, severe hemorrhage is rare and most cases respond to conservative management.

There have been reports of celiac disease developing in women with TS (194, 203, 204), but it is unlikely that it occurs with an increased frequency.

B. Hepatic disease

Recent evidence suggests that women with TS have an increased risk of developing chronic liver disease. Gravholt and colleagues (59) have shown the prevalence of liver cirrhosis in TS to be 5 times that of the general population. In another study of 49 women with TS over the age of 35 yr, 80% had evidence of abnormal liver function (168). There have been several cases reported in the literature associating TS with portal hypertension and either hepatic cirrhosis or fibrosis (205–208). Elevated liver enzymes, particularly γ -glutamyl transferase, have previously been noted by several investigators (168, 209–211). We looked at liver function tests in our clinic population (212). Of 80 women for whom data were available, 35 (44%) had elevated serum liver enzyme concentrations. Data for γ -glutamyl transferase were available for 36 women and it was elevated in 47% of subjects.

The cause of abnormal liver function in TS is unclear, but it does not seem to be related to alcohol excess or infectious hepatitis. We did not show a correlation between abnormal liver function and karyotype, body mass index, or type or duration of HRT (212). It remains unclear as to whether the abnormal liver function is related to an autoimmune process, and the risk of progression to hepatic cirrhosis is unknown. Liver biopsies have revealed a variety of abnormalities ranging from fatty infiltration to hepatic fibrosis and vascular abnormalities. Some authors found liver morphology in women with TS to resemble that of a newborn liver and thus hypothesize that hepatic abnormalities in TS may be due to failure of normal development as a result of lifelong estrogen deficiency (206, 208). We noted a significant improvement in liver function after E2 valerate therapy (212). However, this has not been the experience of other investigators. Wemme and colleagues (209) showed a rise of serum liver enzyme concentrations after therapy with conjugated estrogens, and Masters noted a similar deterioration in liver function in women taking ethinyl E2 (113). Certainly, the use of the combined oral contraceptive pill has been associated with an increased incidence of liver disease (112) but the use of natural estrogens such as E2 valerate has not been shown to adversely affect liver function (213, 214) in women with normal karyotypes and hepatic function. In TS, however, the effect of estrogens on liver function remains controversial. Until this issue is resolved, transdermal estrogens are recommended in those women with elevated liver enzymes, as these have less deleterious effects on hepatic metabolism (170).

XI. Malignancy

The incidence of breast, ovarian, and endometrial cancers does not seem to differ from that of the general population (57, 111). There have been some case reports linking TS with endometrial carcinoma (215–217); however, these were associated with unopposed estrogen therapy. The risk of developing breast or endometrial cancer may increase with the increasing use of sex HRT in women with TS. HRT has obvious benefits to women with TS, which far outweigh the risks, but to reduce the risk of breast or endometrial cancer it is very important that natural estrogens are prescribed in physiological doses and in combination with a progestin.

Gonadoblastoma, an often malignant neoplasm of the dysgenetic gonads composed of cells of stromal and germ cell origin, may develop in females with TS and 45,X/45,XY mosaicism (Section IV.C). The risk of developing gonadoblastoma increases with age and is estimated to be 2% at age 10 yr and 27.5% at age 30 yr (218, 219). Malignant transformation occurs in 60% of these tumors, with 50% developing into dysgerminomas and 10% into other malignant germ cell tumors. Gonadoblastomas vary widely in size, but the larger tumors are more likely to harbor a malignancy (220). They may produce androgens or estrogens, resulting in virilization or feminization, respectively. Early prophylactic excision of the gonads is thus recommended in all Turner mosaics with Y chromosome material detected on routine karyotyping. The exact pathogenesis of gonadoblastoma is unknown. The sharp rise in its incidence after puberty (218) suggests that sex hormones may play a facilitative role in the development of these tumors. Certainly, gonadectomy should ideally be performed before estrogen replacement therapy. It may be postulated that gonadotropins play a stimulatory role in the pathogenesis of gonadoblastoma; however, this is unlikely as other disorders associated with elevated gonadotropins, such as 45,X monosomy and Klinefelter's syndrome, are not associated with an excessive risk of gonadal neoplasia.

Gravholt and colleagues (59) found that women with TS are 5 times more likely to develop cancer of the colon. This is in keeping with an earlier report by Hasle et al. (111), who found the relative risk of colonic cancer in TS to be as high as 6.9. However, there has been a paucity of reports of colonic neoplasia in association with TS in the literature (221, 222). It therefore remains unclear as to whether the association between colonic malignancy and TS is coincidental or whether a real association exists. Although women with TS are at increased risk of IBD, which itself predisposes to colon cancer, IBD did not precede the development of colon cancer in any of the reported cases. The underlying mechanism for an increased risk of carcinoma is therefore speculative. Longstanding estrogen deficiency may play a role in the pathogenesis of colon cancer as ERs are normally found on the colonic mucosa, and epidemiological studies in postmenopausal women suggest that HRT reduces the risk of cancer of the colon (109, 223).

There have been a few cases reported in the literature of females with TS developing leukemia (224–227). However, the incidence of leukemia does not seem to be higher in females with TS. Women with TS do not seem to be at increased risk of developing other malignancies.

XII. Otological Disorders

The congenital craniofacial malformations and consequent distortion of the eustachian tubes and impaired ventilation of the middle ear predispose girls with TS to middle ear infections. Anderson and colleagues (228) were the first to demonstrate this, with 68% of TS girls having had significant otitis media, which was recurrent in more than half of these cases, frequently necessitating surgery. Lippe (5) found that 75% of her patients had recurrent middle ear infections requiring tube insertion for drainage of middle ear fluid and/or an adenoidectomy. Sybert (41) showed that 78% (125/161) of her patients with TS had significant middle ear infections, including 7% who had developed a cholesteatoma. There was a relationship with karyotype: ear problems were least prevalent in women with mosaicism. Similar findings were demonstrated by other investigators (229, 230). Conductive hearing loss consequent to recurrent otitis media is thus a problem in a significant proportion of women. Stenberg and colleagues (230) studied 56 girls with TS aged 4-15 yr and also noted a progressive sensorineural loss in 58% of girls, the youngest being 6 yr old. This was again least frequent in girls with mosaicism. Hultcrantz, Sylven, and colleagues (231, 232) showed a similar abnormality in adults with TS. Deafness has been demonstrated to be progressive with age, with up to 61% of women with TS over the age of 35 yr suffering from significant hearing loss and more than a quarter requiring a hearing aid (168). The cause of sensorineural deafness is unknown, but it is postulated that it may be due to a premature ageing process. Hearing loss due to both sensorineural and conductive deafness appears to be most severe in subjects who lack a short arm of an X chromosome, such as women with 45,X monosomy or isochromosome X, compared with those with mosaicism or partial deletions of Xp (233, 234). Regular audiological evaluation should therefore be routine in view of the high risk of both sensorineural and conductive hearing loss, as deafness can be quite profound before the symptom is volunteered.

XIII. Ophthalmic Disorders

Ophthalmic problems are seen in 63% of women with TS (41). Strabismus is the most common abnormality, present in one third of women (235, 236). Ptosis is present in 16–29% of subjects (235, 236). Other defects that occur with increased frequency in TS include amblyopia and reduced color vision. These abnormalities, thought to occur as a result of fetal lymphedema, often require surgical correction.

XIV. Skin Disorders

Multiple pigmented naevi are very common, affecting 27% of females with TS (5, 237). GH therapy may cause a reversible increase in naevi growth (238), but the clinical significance of this is unclear. The etiology of naevi in TS is unclear but may be related to a neural cell crest defect. In contrast to pigmented naevi developing in karyotypically normal women, sun exposure is not a major determinant of naevi growth in TS (239). There have been two reports of malignant melanoma developing in women with TS (240, 241), but the risk of malignant transformation of melanocytic naevi is not increased in TS (239). Naevi should therefore be removed only if they are located in an area where they are likely to be rubbed by clothing or if malignant transformation is suspected.

Immune-related dermatological conditions such as psoriasis, alopecia, and vitiligo also occur with slightly increased frequency in TS. The prevalence of psoriasis in females with TS is twice that of the general population. Additionally, alopecia areata is 3 times more common in women with TS (5, 41). No obvious correlation with karyotype has been noted, but the number of reported cases is small.

Long-standing estrogen deficiency may result in fine facial wrinkling in untreated women with TS. Finally, women with TS are at increased risk of developing keloid scars after surgery, although the evidence remains anecdotal. They should therefore be counseled about the risk of keloid scars before surgery.

XV. Anorexia Nervosa

Anorexia nervosa affects up to 1% of the general population (242). There have been several reports in the literature suggesting that it occurs with greater frequency in females with TS (90, 243–250). The onset of symptoms often coincides with the onset of estrogen therapy (250–252). No correlation with karyotype has been observed.

XVI. Psychosocial Development

Females with TS have, in general, normal intelligence, the exception being in females with a mosaic karyotype that includes a small ring X chromosome. Migeon and colleagues (253) demonstrated the absence or an abnormality of the X-chromosome inactivation center in tiny ring X chromosomes in females with TS and severe intellectual impairment. Van Dyke *et al.* (254) postulated that the failure of genetic inactivation of the abnormal X chromosome may be responsible for the severity of the phenotype. Zenger Hain and associates (255) showed that in females with a similar karyotype, but in whom the r(X) chromosome was inactivated, intelligence was normal. These results have also been demonstrated by other investigators (256, 257).

A significant number of females with TS have deficits in specific areas of intellectual performance. They usually have normal verbal abilities but impaired nonverbal skills such as visual-spatial processing (258, 259), motor coordination (260–262), and perceptual abilities (263). This may be reflected by poor arithmetic skills, difficulty with constructional tasks, poor sense of direction, and difficulty in learning to drive. They may also have a reduction in short-term memory and attention span (259, 264). Additionally, executive function (the ability to plan and execute multistep tasks) may be impaired in some women with TS (262, 265).

The severity of the cognitive impairment has been shown to be related to the karyotype. Murphy and colleagues (259) demonstrated that females with 45,X monosomy had significantly lower performance scores compared with females with a mosaic karyotype. They also demonstrated differences in brain metabolism between females with TS and controls that correspond to the specific cognitive disabilities (266). Anatomical differences in brain development have also been shown in females with TS independent of karyotype. Murphy *et al.* (267) demonstrated lower hippocampal and right parietal lobe volumes in women with TS and Reiss *et al.* (265) showed a reduction in parietal and occipital lobe volumes in girls with TS. The results of further studies are awaited. It is unclear whether these abnormalities result solely from the X chromosome abnormality or whether they are due to estrogen deficiency. Studies on animals and humans show that estrogens influence brain development in fetal life as well as during puberty, although the mechanisms are unknown. Ross and colleagues (108) studied the effects of estrogen therapy on motor function and nonverbal abilities in girls with TS. They found that estrogen-treated girls performed nonverbal and visual-motor tasks much quicker than nontreated girls. Ross and colleagues (268) also studied the effect of GH therapy on cognitive function in girls with TS but failed to find a significant difference after therapy. It is likely that some of the areas of cognitive deficits are directly due to the X chromosome abnormality, as evidenced by differences in verbal and visuospatial function between females with 45,X monosomy and mosaics (259) and other areas of cognitive deficits, such as memory and reaction time, are as a result of estrogen deficiency and are therefore potentially reversible. Skuse and colleagues (269) postulated that an imprinted gene on the X chromosome that escapes X inactivation influences cognitive abilities and social functioning, i.e., a gene may result in different cognitive abilities depending on whether it is inherited from the mother or father. They showed that 45,X females with TS with a paternally derived X chromosome had superior verbal and executive skills compared with girls whose X chromosome was maternally derived. However, this study must be interpreted with caution, as cognitive function was assessed by parental report only, variations in the age range were not corrected for, and the study has yet to be replicated by others. Certainly, Haverkamp et al. (270) did not find a significant difference between girls with TS and their age-matched siblings on formal cognitive testing.

Despite these problems, a significant number of women with TS complete a university degree, and the majority of women have little difficulty in finding employment. Sybert (41) found that 33% of adults with TS went to university compared with 19% of other American females, and 10% had a postgraduate degree. Similar findings have been reported from Japan (271). Similarly, in our clinic population, where data were available for 198 women, 69 (35%) were studying at university or had attained a university degree. However, women with TS are often employed in jobs for which they are overqualified (41, 168). The reasons for this are unclear. Interestingly, a significant number of women enter childcare or healthcare professions such as nursing and nursery nursing (Table 10).

Finally, females with TS tend to have characteristic personality traits. They find it more difficult to make friends and enter into sexual relationships. This may be due, in part, to difficulty in understanding nonverbal communication but also could be due to poor self-image as a result of short stature and delayed sexual maturation. Delooz *et al.* (272) showed poor self-image in 50% of adults with TS. Similar results were seen by other groups (155, 273) as well as in adolescent girls with TS (261). Self-esteem and psychological well being in adulthood may be enhanced in women who started estrogen replacement therapy before the age of 14 yr (274). Sylven and colleagues (168) showed that of 49 women over the age of 37 yr, only 31 (63%) ever married. Corresponding figures for Sybert (41) and Holl *et al.* (155) were 27% and 4%, respectively. Several investigators have also found that females with TS tend to leave home and become sexually active at a later age than their peers (41, 275).

Women with TS should therefore have access to clinical psychologists who are aware of the specific areas of deficiencies relevant to females with TS, as well as being able to counsel them about anxieties relating to short stature, infertility, and sexual relationships.

XVII. Conclusions

Women with TS are at risk for a number of medical problems that require care throughout adulthood. After the completion of puberty and growth treatment, women with TS should be followed up by a multidisciplinary team equipped to manage the specific medical problems associated with the syndrome. As much of the long-term morbidity associated with TS comes into the domain of endocrinology, it is necessary for endocrinologists to become skilled in other aspects of the syndrome to provide a holistic approach to long-term care. Ideally, access to a dedicated cardiologist, ear nose and throat surgeon, audiologist, psychologist, and fertility specialist should be made available in one clinic so that the adult service is built to the needs of the syndrome rather than the other way round. Attendance of a member of a patient advocacy group such as the Turner Syndrome Society (Table 11) may also provide additional support. Cardiovascular disease remains an important preventable cause of excessive morbidity and mortality in TS, monitoring of which must be coordinated with fertility treatments and estrogen replacement regimens. A suggested schedule of basic monitoring is presented in Table 12, although individuals with specific needs may need a more intensive approach. With increasing awareness of these issues and the development of more dedicated clinics, there is every prospect that improved life expectancy and quality of life can be achieved.

There remain several unresolved issues in the pathogen-

TABLE 10. Occupation Group of 198 adults with TS attending the Turner clinic at the Middlesex Hospital, UK

Occupation group	No. (%)
Health, domestic, and childcare	58 (30)
Secretarial	17(8.5)
Clerical	15(7.5)
Sales and catering	15(7.5)
Arts	15(7.5)
Professional	14(7)
Business/management	10(5)
Civil service and government	8 (4)
Teaching	8 (4)
Finance	4(2)
Student	20 (10)
Unemployed	14(7)

TABLE 11. Recommended TS support groups

Support group	Website address
The Turner Syndrome Society of	www.turner-syndrome-us.org
the United States	
Turner Syndrome Support	www.tss.org.uk
Society, UK	

TABLE 12. Suggested follow-up of adults with TS

Baseline
Karyotype
Renal and pelvic ultrasound
Echocardiography
Thyroid autoantibodies
Gonadotropins
Annual
Physical examination (BMI, blood pressure, CVS, etc.)
Thyroid function
Fasting lipids
Fasting blood glucose
Liver function
Renal function
3–5 Yearly
Echocardiography
Bone densitometry
Audiogram

BMI, Body mass index; CVS, cardiovascular system.

esis and management of TS. The gene(s) responsible for the bone disorders, premature ovarian failure, and other features of TS have yet to be elucidated. Preliminary studies on the effects of estrogen replacement therapy on colonic cancer and cognitive function have yielded tantalizing results, but further work is necessary. Long-term data looking at the natural history of aortic root dilatation are required. Finally, the association of the isochromosome X karyotype with autoimmune thyroid disease and inflammatory bowel disease provides an exciting model from which to study the genetics of autoimmune diseases.

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Low thyroid reserve due to autoimmune thyroiditis is increasingly recognized as a serious health problem. In the field of type 1 diabetes mellitus it has already been a goal for several years to try and attenuate the destructive autoimmune—insulitis—process. Because of recent developments in basic and clinical immunology, the organizers of the meeting found the time appropriate to bring together experts in the fields of thyroid and islet autoimmunity, early detection of endocrine autoimmune diseases, and tolerance induction. We hope for a cross-fertilization during the discussions of above-described topics. There will be ample time for such discussions during oral and poster presentations and plenary sessions.

Lectures (approximately 10–12) are by invitation of the Organizing Committee. Abstracts must be sent to the Organizing Committee; eight abstracts will be selected for oral presentation.

For further information and submission of abstracts please contact: Prof. Hemmo A. Drexhage, Department of Immunology, Erasmus University Medical Center Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands, Phone 31-10-408.8188, Fax 31-10-408.9456, E-mail: moerland@immu. fgg.eur.nl; or one of the other members of the organizing committee: Dr. Alex F. Muller (Department of Internal Medicine, Diakonessenhuis, Utrecht, The Netherlands, E-mail: amuller@diakhuis.nl), Dr. Arie Berghout (Department of Internal Medicine, MCRZ, Rotterdam, The Netherlands, E-mail: berghouta@mcrz.nl), Prof. Theo J. Visser (Department of Internal Medicine, EMCR, Rotterdam, The Netherlands, E-mail: visser@inw3.azr.nl).

> Second International Symposium on Progestins, Progesterone Receptor Modulators, and Progesterone Antagonists Siena (Italy) 20–23 November, 2002 www.unisi.it/eventi/progestins

Topics to be reviewed include: Mechanism of Action, Progesterone Receptors and their Isoforms, Pharmacology, Target Tissue Effects, Clinical Applications, Contraception, and Controversial Issues Related to Progestin Treatment.

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