FERTILITY AND STERILITY

Vol. 30, No. 1, July 1978
Printed in U.S.A.

AMENORRHEA—ETIOLOGIC APPROACH TO DIAGNOSIS

PAUL G. McDONOUGH, M.D.

Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta, Georgia 30901

A delay in the initiation of menses at the time of puberty or the interruption of an established menstrual pattern constitutes amenorrhea. Cessation of menses normally occurs in the human female at the time of menopause. Failure to initiate menses, interruption of a normal cyclic pattern of menses, or premature cessation of menses constitutes unphysiologic amenorrhea. Arbitrarily classifying menarchal failure and the interruption of a normal cyclic menstrual pattern into primary and secondary amenorrhea is largely semantic, since the same etiologic factors may be operative in either instance.

The average age for first menses is 13.5 years. Menarche at chronologic ages 11 and 15 are 2 standard deviations removed from the mean.[1] The mean for the normal ovulatory menstrual interval is 28 days, and ranges around that interval extend from 21 to 44 days.[2] The average age for cessation of menses is 49, with ranges from 35 to 55 years. Departure from these norms constitutes at least temporary failure of the cycling mechanism with clinical amenorrhea. An arbitrary rule of thumb as to what constitutes significant pathologic amenorrhea is difficult to define and has very little use clinically. It is the concern or anxiety of the patient, regardless of the duration of amenorrhea, that prompts her visit to the physician. For example, interruption of the cycling mechanism due to pregnancy should be diagnosed as soon as possible. A delay of 3 to 6 months in the diagnosis of other causes of amenorrhea does not create any harm or undue anxiety for the patient if the presence of pregnancy or trophoblastic disease has been eliminated. All types of normally and ectopically located trophoblastic proliferations should be thought of collectively and suspected in every patient who has a positive test for human chorionic gonadotropin. If suspicion of trophoblast persists in spite of a negative routine pregnancy test, then the more sensitive β-subunit human chorionic gonadotropin determination should be performed. Excluding the presence of active, viable, proliferating trophoblast in all patients with amenorrhea should be the first consideration before other etiologies are considered.

Over the past decade the evaluation of amenorrhea has been assisted by advances and refinements in diagnostic techniques. The diagnosis of ovarian failure has been facilitated by the availability of sensitive serum gonadotropin measurements. Improved techniques of chromosomal banding ensure a confident diagnosis of the sex chromosome abnormalities associated with amenorrhea. Laparoscopic techniques have provided an easy means of visualizing the gonads, and polytomography of the sella turcica assisted by computerized axial tomography (the CAT scan) has improved the early diagnosis of pituitary tumors. A specific radioimmunoassay for serum prolactin has provided a sensitive indicator of hypothalamic-pituitary dysfunction and prolactin-secreting pituitary microadenomas. Plasma levels of testosterone, growth hormone, and cortisol are readily available through commercial laboratories. The general trend is toward the direct measurement of pituitary polypeptides and steroids in blood rather than their counterparts or metabolites in urine. This general switchover from urine to blood and from milligrams to nanograms and picograms has created a new dimension that the physician must master. Lastly, the isolation of gonadotropin-releasing

Received January 3, 1978.
*Reprint requests: Paul G. McDonough, M.D., Department of Obstetrics and Gynecology, Medical College of Georgia, 1120 15th Street, Augusta, Ga. 30901.

hormone (GnRH) and other potent analogs provides for a dynamic test of hypothalamic-pituitary function.

In spite of these improvements in diagnostic techniques, a careful history and physical examination with appropriately selected laboratory studies remain paramount in the evaluation of amenorrhea. The clinician's acumen should include a perspective of the different etiologies of amenorrhea, their relative frequency, and an acute awareness of any particular causes which may compromise the life-span or fertility of the patient.

ETIOLOGY

The etiologies of amenorrhea which preclude menarche tend to be represented by genetic causes or anatomical maldevelopments of the genital tract. In contrast, the interruption of an established cyclic pattern of menses is usually psychogenic in origin. One should appreciate the high frequency of genetic causes in the patient with primary amenorrhea and the relatively high frequency of psychogenic factors in patients with secondary amenorrhea. The approach to an evaluation of these high-frequency groups will be stressed.

The spectrum of pathology seen in association with amenorrhea is varied, but certain well-defined categories are recognizable. These categories can be broadly grouped into eugonadotropic amenorrhea, hypergonadotropic amenorrhea, hypogonadotropic amenorrhea, and amenorrhea occurring in association with androgen excess (Table 1). The separation of the amenorrheas into these four large groups facilitates the diagnosis. The first two groups are more often associated with menarchal delay, whereas the hypogonadotropic group usually presents with secondary amenorrhea. Disorders of androgen excess may produce primary or secondary amenorrhea, but are more frequently associated with the latter.

TABLE 1. *Etiology of Amenorrhea*

Eugonadotropic amenorrhea
Nonfunctional uterus
Congenital (Rokitansky syndrome)
Acquired (Asherman's syndrome)
Functional uterus with obstruction
Hypergonadotropic amenorrhea
Chromosomally incompetent ovarian failure (CIOF)
Chromosomally competent ovarian failure (CCOF)
46,XY forms
Swyer's syndrome (XY gonadal dysgenesis)
Congenital androgen insensitivity syndrome
46,XX forms
Autosomal recessive gene
Environmental factors
Autosomal abnormalities
Infectious infiltrative disease
Autoimmune disease
Gonadotropin-resistant ovary (Savage syndrome)
17-Hydroxylase deficiency
Hypogonadotropic amenorrhea
Congenital (Kallmann's syndrome)
Acquired
Pituitary tumors and necrosis
Drug-induced amenorrhea
Psychogenic amenorrhea
Stress-induced tonic LH (short-term)
Stress-induced tonic LH (long-term)
Hypogonadotropism (stress, nutrition)
Hypogonadotropic hyperprolactinemia
Systemic illness—endocrine
Thyroid (hyper, hypo)
Adrenal (hyper, hypo)
Systemic illness—non-endocrine
Amenorrhea and galactorrhea
Androgen excess
Adrenal tumor
Congenital adrenal hyperplasia
Virilizing ovarian tumors
Androgenic ovary syndrome

Eugonadotropic Amenorrhea

Nonfunctional Uterus

Congenital.

The most frequent anatomical cause of primary amenorrhea is the Rokitansky-Kuster-Hauser syndrome.[3,4] This syndrome is characterized by hypoplasia and failure of fusion of the two Müllerian anlagen. The bilateral hypoplastic discrete uteri seen in these individuals are associated with total vaginal agenesis. Ovarian endocrine function and exocrine function are normal. The failure of the two Müllerian anlagen to fuse completely eliminates the natural stimulus for normal canalization of the vagina by upgrowth of urogenital sinus epithelium. Developmental abnormalities of the kidneys occur frequently in these individuals. The most frequent renal malformation is a solitary ectopic kidney located in the pelvis. Skeletal abnormalities such as mild to severe scoliosis and Klippel-Feil deformity occasionally occur in association with the Rokitansky-Kuster-Hauser syndrome. The etiology of this syndrome remains obscure. The high frequency of sporadic cases tends to incriminate an autosomal recessive gene or an environmental factor affecting early development of the mesonephric and paramesonephric system. Identical twins discordant for Rokitansky-Kuster-Hauser syndrome have been reviewed by Lischke et al.[5] Discordance

in monozygotic twins suggests that differential environmental factors are operative in utero.

Individuals with the Rokitansky-Kuster-Hauser syndrome are usually asymptomatic except for menarchal delay, and present with normal somatic and sexual development. Total absence of the vagina or the presence of a small vaginal pouch is usually the only physical finding. Cytogenetic studies confirm a normal 46,XX karyotype, and the basal body temperature graph is biphasic. The occurrence of normal adrenarche and normal female levels of serum testosterone exclude the diagnosis of congenital androgen insensitivity or testicular feminizing syndrome. The diagnosis of Rokitansky-Kuster-Hauser syndrome can usually be made clinically, and laparoscopic visualization of the pelvic structures is not a necessity. An intravenous pyelogram, however, should be performed in all patients with a presumed diagnosis of Rokitansky-Kuster-Hauser syndrome because of the high incidence of associated renal malformations. Extirpation of the rudimentary uterine tissue is not necessary. These uteri are rarely the site of malignancy, uterine fibroids, covert hematometra, or symptomatic herniation into the inguinal canal. A vagina can be created for these patients by utilizing the Frank technique.

Acquired.

Patients with Asherman's syndrome also have normal ovarian function as evidenced by normal levels of gonadal steroids and a biphasic basal body temperature chart. The amenorrhea is caused by intrauterine adhesions that partially or completely obliterate the uterine cavity. These adhesions are usually caused by overzealous postpartum curettage or induced abortions complicated by endometritis.[6] Bleeding does not occur after estrogen-progesterone treatment, and the diagnosis can be confirmed by hysterography or hysteroscopy and by obtaining characteristic fibrous tissue at curettage. The exact incidence of endometrial sclerosis, or Asherman's syndrome, is not known but it probably constitutes a small percentage of patients with amenorrhea.

Tuberculosis may occasionally cause sufficient endometrial scarification to provide target-organ or anatomical amenorrhea. In some instances the destruction of the endometrium will produce sclerotic changes without any significant distortion of the intracavitary portion of the uterus on hysterosalpingography. Hysteroscopy, in experienced hands, may be necessary for the proper diagnosis. On a few occasions after a missed abortion, nonviable hyalinized or calcific villi may remain in the uterus and produce anatomical amenorrhea. Pregnancy testing is negative in these patients, and endometrial biopsy or curettage is necessary to establish the diagnosis.

A form of endometrial refractoriness due to temporary involution of the endometrial glands may occur following discontinuation of oral contraceptives or after the use of injectable synthetic steroids such as Depo-Provera. This form of amenorrhea, due to target-organ unresponsiveness, needs to be distinguished from the hypothalamic-pituitary oversuppression syndrome produced by oral contraceptives.

Functional Uterus with Obstruction

Among patients with amenorrhea secondary to an obstructed genital tract, patients with an imperforate hymen or a transverse vaginal septum constitute the largest group. The vast majority of patients with an obstructed genital tract present with primary amenorrhea; however, acquired obstruction of the genital tract with secondary amenorrhea may occur following cervical conization or as the result of a cervical or uterine malignancy.

Imperforate hymen is esaily diagnosed by the clinical constellation of normal sexual development, pelvic pain, urinary frequency, and the presence of a bulging mass on the perineum with the Valsalva maneuver.

Transverse vaginal septum, which represents a failure of canalization of the distal third of the vagina with a proximal hematocolpos and hematometra, is not always precisely recognized.[7] Transverse vaginal septum tends to occur in siblings, as evidenced by two sets of affected siblings in patients whom we have studied.[4] The frequent familial occurrence of transverse vaginal septum in consanguineous pedigrees suggests a genetic etiology, probably autosomal recessive inheritance. Renal malformations may accompany a transverse vaginal septum but not with the same frequency as in the Rokitansky-Kuster-Hauser syndrome. Patients with a transverse vaginal septum experience obstructive symptomatology of the genital tract and accompanying bladder irritability. The pelvic pain symptoms may be misdiagnosed as appendicitis in this age group unless a pelvic examination is performed. Patients with a transverse vaginal septum have a firm pelvic mass which is not always symmetric in outline. Visual inspection of the introitus reveals no

apparent vagina and no change in perineal contour or distention of the introitus with the Valsalva maneuver. The latter is important in distinguishing a transverse vaginal septum from an imperforate hymen. A transverse vaginal septum is rigid and presents a solid core of uncanalized tissue extending over the last 3 to 5 cm of the lower vagina. The proximal vagina, distended with trapped menstrual blood, can be felt on rectal examination. Treatment of a transverse vaginal septum involves surgical dissection of the uncanalized distal vagina, identification of the patent upper vagina, and mobilization of tissue sufficient to bring the upper vagina down to the level of the introitus. Care is necessary to prevent the newly formed vagina from assuming a disfiguring hourglass deformity that interferes with coitus. Diagnostic needling of any obstructed genital tract should be performed only prior to definitive surgical correction. Preliminary needling without definitive plans for surgery may convert a proximal hematocolpos into a proximal pyocolpos.

Delays in the diagnosis of amenorrhea due to genital tract obstruction will result in continued menstrual reflux. An aseptic inflammatory process with accompanying endometriosis can permanently impair future fertility. The diagnosis of an obstructed genital tract is one of the few amenorrhea emergencies. Delays in the diagnosis of Rokitansky-Kuster-Hauser syndrome, or total vaginal agenesis, do not pose a similar threat since permanent infertility is already present secondary to hypoplasia of the Müllerian system. Nevertheless, early diagnosis of total vaginal agenesis does help to prepare the patient for the development of a neovagina and provides for a frank unequivocal discussion of her sterility.

The presence of eugonadotropic amenorrhea clearly emphasizes the necessity for visual inspection of the introitus and palpation of the cervix. All eugonadotropic patients with biphasic basal body temperature charts and secondary amenorrhea should undergo sounding of the uterus and hysterosalpingography or hysteroscopy performed to rule out endometrial sclerosis or Asherman's syndrome. If hysterography is normal, an endometrial biopsy should accompany these studies in order to rule out instances of protracted missed abortion with residual, nonactive trophoblastic tissue. Endometrial tuberculosis is a rare target-organ disease, but histologic and fluorescent studies help to identify the bacterium.

Hypergonadotropic Amenorrhea (Primary Ovarian Failure)

Increasing numbers of patients with amenorrhea are being identified as having hypergonadotropic ovarian failure. The identification of these patients has been aided by the availability of sensitive assays for serum gonadotropins, improved cytogenetic techniques, and the widespread use of the laparoscope as a technique of gonadal visualization. The statistical importance of this group of patients with primary ovarian failure should be appreciated when evaluating patients with hypoestrogenic forms of amenorrhea. In the past, the major cause of ovarian failure has been attributed to the Turner or quasi-Turner phenotypes with demonstrable sex chromosome abnormalities. Radioimmunoassay techniques for serum gonadotropins have enabled identification of increasing numbers of phenotypically and cytogenetically normal 46,XX females with amenorrhea and primary ovarian failure (Fig. 1).[8] The precise relationship between 46,XX females with primary ovarian failure and those with structural abnormalities of the sex chromosome remains to be clarified. This entire group of patients, both those with normal chromosomes or chromosomally competent ovarian failure (CCOF) and those with abnormal chromosomes or chromosomally incompetent ovarian failure (CIOF), tend to be categorized as patients with gonadal dysgenesis or rudimentary streak gonads. The implication is that a genetic etiology is responsible even in chromosomally normal individuals with primary ovarian failure. The latter remains to be clarified. It is conceivable that phenotypically normal, chromosomally competent,

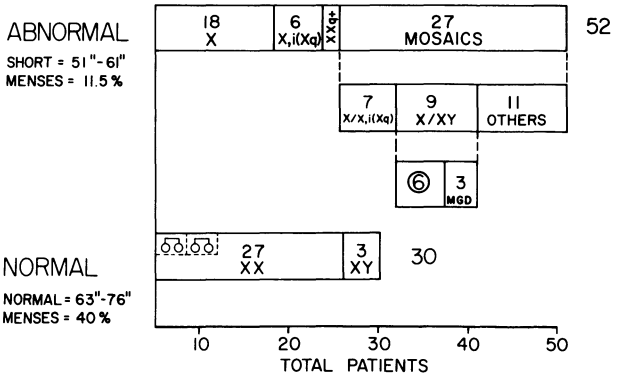

FIG. 1. Sex chromosome constitutions in 82 patients beyond 12 years of age with primary ovarian failure. The *circled 6* represents six 45,X/46,XY mosaics with rudimentary streak gonads who are nonmasculinized. The other three 45,X/46,XY individuals are masculinized with sexual ambiguity. MGD, Mixed gonadal dysgenesis. ♂ ♀, Sisters. (Reproduced with permission from reference 8.)

forms of gonadal dysgenesis represent a heterogeneous group of individuals with diverse etiologies. The nexus for the clinician between the cytogenetically normal and abnormal forms of gonadal dysgenesis is gonadal failure. The measurement of serum gonadotropins provides the physician with a common reference point in the approach to this group of patients who present with ovarian failure, either at the time of anticipated menarche or as secondary amenorrhea later in life. Patients with primary ovarian failure and amenorrhea can be placed into these two distinct clinical categories on the basis of the cytogenetic findings.

Ovarian Failure with Abnormal Chromosomes—Chromosomally Incompetent Ovarian Failure (CIOF)

A spectrum of sex chromosome karyotypes ranging from 45,X to 45,X/46,XX and 45,X/46,XY has been described in these individuals. Short stature is the principal clinical finding in individuals with primary ovarian failure and structural abnormalities of their sex chormosomes (Fig. 1).[8] Other associated somatic anomalies such as webbed neck or shield chest may or may not accompany the diminished stature. These minor somatic anomalies and short stature may be valuable clues as to the presence of a sex chromosome abnormality in the prepubertal child. Beyond the time of anticipated menarche, regardless of somatic phenotype, unequivocal laboratory evidence of hypergonadotropic ovarian failure is the convergence point for diagnosis. Patients with totally absent or limited ovarian function and structural privations of the sex chromosomes are collectively categorized as having gonadal dysgenesis. It is logically assumed that the privation of sex chromosomes is etiologically linked to the presence of anatomical streak gonads and functional ovarian failure.

A demonstrable deletion of genetic material in the sex chromosome constitution still constitutes the most frequent cause of hypergonadotropic amenorrhea (Fig. 1).[8] The predominant chromosomal abnormality in this group of patients is sex chromosome mosaicism. The most frequent combinations have been 45,X/46,X,i(Xq) and 45,X/46,XY. The latter group is important because of its relative frequency among mosaic patients with ovarian failure, and identification of the Y chromosome in a phenotypical female requires prophylactic extirpation of the rudimentary streak gonads. Although 45,X still constitutes the principal single cell-line chromosome abnormality in patients with ovarian failure, six 45,X/46,XY individuals have been identified who are nonmasculinized Turner or quasi-Turner phenotypes with bilateral streak gonads (Fig. 1, *circled 6)*.[8] The sporadic identification of such nonmasculinized individuals emphasizes the need to search diligently for a Y cell line in all Turner or quasi-Turner phenotypes with ovarian failure, regardless of the presence or absence of masculinization. This cytogenetic search should include adequate cell counts. Utilization of currently available fluorescent techniques to identify the Y body is important. However, this is not a satisfactory answer to the dilemma, since only the genetically inert portion of the Y chromosome fluoresces intensely with quinacrine hydrochloride. Perhaps future techniques to identify Y genetic material, such as the immunologic determination of H-Y antigen, may assist in the identification of patients who are at risk for dysgenetic gonadal tumors.[9] Awareness of the scope and limitations of our present techniques for identifying nonfluorescent, genetically active, Y material dictates that all chromosomally abnormal amenorrheic patients be followed closely with pelvic examination and periodic x-rays of the pelvis in order to detect an early dysgenetic ridge tumor in patients with an unrecognized Y cell line. Periodic x-rays of the pelvis in such individuals provide for the early detection of calcification that indicates the presence of a gonadoblastoma.[10]

With rare exceptions, privations or deletions of sex chromosome material tend to diminish stature regardless of the portion deleted. Most patients with hypergonadotropic ovarian failure and chromosomal deletions tend to be less than 63 inches tall.[8, 11] The combination of short stature and primary ovarian failure seems to be causally related to privations or deletions of sex chromosome material. Normal stature and cytogenetic competence, either 46,XX or 46,XY, tend to go hand in hand.

Among patients with chromosomally incompetent ovarian failure who menstruate, it is not possible to draw any correlation between sex chromosome morphology and primary or secondary amenorrhea. This reflects the lack of an all-or-none phenomenon in those factors affecting ovarian hypoplasia.[12] This broad spectrum of ovarian function probably represents varying degrees of interference with germ-cell migration, mitotic activity in the genital ridge, abnormal meiotic pair-

ing, or overutilization of primary oocytes. The degree of interference with each of these events cannot be specifically related quantitatively to the deletion of sex chromosome material.

In addition to recognizing hypergonadotropic amenorrhea, the principal responsibilities of the physician to the chromosomally abnormal, short-statured group are identification of cardiovascular renal malformations, extirpation of rudimentary streak gonads in patients with a Y cell line, and continued surveillance for ridge tumors in all patients through careful periodic examination and roentgenographic studies of the pelvis.

Ovarian Failure with Normal Chromosomes—Chromosomally Competent Ovarian Failure (CCOF)

The majority of patients with ovarian failure and normal 46,XX or 46,XY karyotypes tend to be referred to collectively as having pure gonadal dysgenesis. They have been grouped under the spectrum of gonadal dysgenesis because their gonadal morphology is frequently similar to the rudimentary streak gonads seen in the Turner or quasi-Turner phenotypes. This category probably encompasses a large heterogeneous group of patients in whom different etiologies are involved in the production of ovarian failure.[11, 12] In this discussion, "chromosomally competent ovarian failure" describes individuals with ovarian failure who are phenotypically and cytogenetically normal. Historically, patients in this group were identified along with chromosomally abnormal individuals. Initially their number was small and, because of their cytogenetically abnormal counterparts, an unrecognized genetic etiology was presumed. The development of sensitive radioimmunoassay techniques to measure serum gonadotropins has expanded the scope of the enigma. Measurements of serum follicle-stimulating hormone (FSH) in hypoestrogenic females with amenorrhea, regardless of phenotype or previous ovarian function, have increased the frequency of diagnosis of ovarian failure in phenotypically and cytogenetically normal females.

Among 82 individuals with hypergonadotropic amenorrhea, 30 had normal 46,XX or 46,XY karyotypes and normal stature (Fig. 1).[8] Since many individual patients with chromosomally competent ovarian failure probably are not reported, it is conceivable that this group may be larger than is apparent from the literature. Patients with normal chromosomal complements (46,XX or 46,XY) tend to be tall, since epiphyses stay open in the absence of ovarian steroids and the presence of a normal genetic complement. The normal chromosomal karyotype ensures normal stature which is further augmented by delayed epiphyseal fusion as a result of primary ovarian failure. Secondary amenorrhea was the presenting complaint in 40% of the individuals with chromosomally competent ovarian failure (Fig. 1). To establish the diagnosis of chromosomally competent ovarian failure, serum FSH levels should be determined in each hypoestrogenic female with either primary or secondary amenorrhea. An elevated immunoreactive serum FSH on two consecutive determinations can be considered diagnostic of primary ovarian failure and should at least prompt a buccal smear to distinguish the cytogenetically normal 46,XX and less frequent 46,XY forms of gonadal failure.

46, XY Forms.

Swyer's Syndrome (XY Gonadal Dysgenesis). Chromosomally competent forms of gonadal failure with XY karyotypes are infrequent but important to keep in mind because of the high risk of dysgenetic ridge tumor and to avoid confusion with forms of androgen insensitivity syndromes. Chromosomally competent XY ovarian failure seems to be inherited as a sex-linked gene.[13] Individuals with XY forms of gonadal dysgenesis should have prophylactic extirpation of the rudimentary streak gonads because of the high frequency of tumor formation. Extirpation should be performed once the Y material is identified, since tumor formation may occur at any age. The palpation of a cervix or Müllerian system and the presence of sexual infantilism and low-normal serum testosterone levels in these patients serve to differentiate XY gonadal dysgenesis (Swyer's syndrome) from testicular feminizing syndrome.[14]

Congenital Androgen Insensitivity Syndrome. Patients with the congenital androgen insensitivity syndrome (testicular feminizing syndrome) have only slight elevations of serum gonadotropin levels and are gonadal males. Testicular tissue in these individuals is active is suppressing Müllerian development. In spite of adequate androgen production, cytosol receptors for testosterone are defective, and a hairless phenotype is present. Both XY forms of gonadal dysgenesis and XY androgen insensitivity syndromes probably represent a spectrum of male pseudohermaphroditism. It is important to be able to recognize both forms among a group of patients with primary amenorrhea because of the necessity for removal of the

rudimentary streak gonads in the case of XY gonadal dysgenesis and the intra-abdominal testes in the case of testicular feminizing syndrome.

46,XX Forms.

The diverse etiology of ovarian failure in phenotypically normal 46,XX individuals should be appreciated. Although familial instances of this entity occur, a heterogeneous group of causes probably accounts for the sporadic cases.[11] The diverse etiologies of chromosomally competent ovarian failure with a 46,XX karyotype are listed in Table 2.

The presence of multiple affected siblings and the frequency of consanguinity, associated neuroauditory abnormalities, and XX cells in gonadal culture indicate that some XX forms of ovarian failure are distinct genetic entities and are probably related to a single autosomal recessive gene.[15] The report of identical twins discordant for ovarian failure suggests that environmental factors may be operative in some instances.[16] These environmental factors could prevail in utero or could represent an environmental insult occurring later in neonatal life or in early infancy. Environmental factors could prevent migration, interefere with early mitotic activity in the gonadal ridge, disrupt meiotic pairing, or destroy the follicular apparatus of the fully developed ovary. The precise contribution of environmental factors will be ascertained only by careful historic scrutiny of all sporadic cases of ovarian failure. In a few instances autosomal chromosomal aberrations have been identified in some individuals with ovarian failure. In most instances these aberrations represent normal variants of chromosomal morphology that are not related to the gonadal problem. However, the modifying role of autosomal variants or abnormalities in otherwise chromosomally intact humans with ovarian failure is speculative at present.[17] Rarely, systemic diseases such as β-thalassemia and mucopolysaccharidosis may account for enough infiltration to the ovary to produce ovarian failure. The etiology in these instances is apparent in the ovarian histology. Autoimmune ovarian failure is difficult to document unless associated with multiglandular endocrinopathy. Autoimmune ovarian failure should be suspected principally when ovarian failure is identified in a patient with normal chromosomes, in association with a pluriglandular endocrine disorder.[18] A small number of patients may have functional ovarian failure but exhibit large numbers of primordial follicles on ovarian biopsy. This group of patients, speculated to have an ovarian cell membrane receptor defect, have been described literally in the expression "ovarian insensitivity syndrome" or "Savage syndrome," after the original case study.[19] The receptor defect, if present, does not seem to be an all-or-none phenomenon as judged by the degree of breast development described in some patients with the Savage syndrome. Further studies may help to elucidate the nature of the abnormality and to establish whether the gonadotropin-resistant ovary represents a distinctly unique form of ovarian failure.[20]

TABLE 2. *Causes of Chromosomally Competent 46,XX Ovarian Failure (CCOF)*

Autosomal recessive
Environmental factors
Autosomal abnormalities
Infectious (infiltrative disease)
Autoimmune disease
Gonadotropin-resistant ovary (Savage syndrome)
17-Hydroxylase deficiency

A deficiency in 17-hydroxylation which prohibits the production of androgens, estrogens, and some adrenal steroids can be considered a rare cause of hypergonadotropism. As a consequence of this abnormality in steroidogenesis, these patients have increased levels of deoxycorticosterone and progesterone. The absence of circulating estrogens results in elevated gonadotropin levels.[21]

Amenorrhea caused by ovarian failure is basically a functional or biochemical diagnosis. Serum gonadotropin measurements should always precede ovarian visualization and biopsy. One should not place undue reliance on ovarian morphology and histology. The morphology of ovarian hypodevelopment is varied and may resemble that of ovaries in hypogonadotropic hypogonadism even to the experienced eye. A functional diagnosis of primary ovarian failure is a better index to the disturbance level than are subjective interpretations of ovarian morphology and histology.

Hypogonadotropic Amenorrhea

The third category of patients with amenorrhea is represented by patients with low or undetectable base line gonadotropin levels. Low levels of pituitary gonadotropins are seen in the prepubertal child, but low or absent gonadotropins are unphysiologic once hypothalamic maturity has occurred. In some patients, hypothalamic-pituitary

maturity is never achieved, and a peristent, irreversible form of hypogonadotropism persists. Other patients with hypogonadotropism are initially normal but develop acquired hypogonadotropism as a result of diverse etiologies. Included in the latter category are patients with low base line FSH and luteinizing hormone (LH) levels and some patients with hypothalamic-pituitary dysfunction who have low serum FSH and tonically elevated serum LH.

Congenital Hypogonadotropism (Kallmann's Syndrome—Irreversible Hypogonadotropism)

Irreversible or monotropic failure of gonadotropins is referred to as Kallmann's syndrome or isolated gonadotropin deficiency. These patients are unable to achieve effective synthesis of gonadotropins, presumably because of a defect in the hypothalamus. They also may have olfactory sensory defects. The nature and extent of the olfactory defects are determined in effect by the working definition of anosmia, since the spectrum of normal odor detection varies considerably from one examiner to another. For diagnostic purposes it is therefore more important to focus on the persistently low gonadotropin levels.[22] A single-dose challenge with GnRH in such patients usually results in no gonadotropin release. In some patients with Kallmann's syndrome repeated challenges or constant infusions of GnRH may result in a blunted gonadotropin response.[23] The abbreviated response to GnRH stimulation noted especially in gonadotropins measured in pooled urine samples is sufficient to further the argument as to whether the defect is hypothalamic or pituitary in origin.[24] Perhaps further studies of dynamic hypothalamic-pituitary function will serve to delineate the anatomical area of dysfunction. Other genetic syndromes such as Prader-Willi and Laurence-Moon-Biedl are associated with irreversible hypogonadotropism but are exceedingly rare, and other aspects of the syndrome (principally mental retardation) supercede the hypogonadotropism in importance.

Acquired Hypogonadotropism

Pituitary Tumors and Pituitary Necrosis.

Central nervous system lesions associated with acquired hypogonadotropism are most frequently pituitary and/or parapituitary tumors. Galactorrhea may be seen in association with amenorrhea in some of these patients. It is important to recognize pituitary tumors because they pose a threat to the life of the patient and curability is directly related to the time of diagnosis. The most common pituitary tumor producing amenorrhea in the younger age group is craniopharyngioma, which may grow rapidly into the suprasellar area. Fortunately, most craniopharyngiomas calcify and are usually apparent on routine x-rays of the sella turcica. The rapid growth of this tumor makes periodic skull x-rays imperative in all patients with either menarchal delay or limited early menstrual function. Other pituitary tumors, such as chromophobe adenomas and prolactin-producing adenomas, tend to grow slowly over a longer period of time. Amenorrhea alone or amenorrhea in association with galactorrhea may antedate the neurologic symptomatology by many years. Radiologic views of the sella turcica and determinations of serum prolactin are important diagnostic adjuncts in the follow-up of all patients with persistent hypogonadotropism. Hypogonadotropism accompanied by hyperprolactinemia is an indication for further studies of the central nervous system, including polytomography of the sella turcica, examination of visual fields, and computerized axial tomography.

Persistent hypogonadotropic hyperprolactinemia may also occur in association with growth hormone and adrenocorticotropic hormone (ACTH)-producing pituitary tumors. Careful physical examination is important in all amenorrheic patients in order to detect signs of hormone or cortisol excess. Growth hormone levels should be measured in the morning before and after 30 minutes of exercise. High basal levels of growth hormone and parodoxical responses to stimulation and suppression studies should prompt further radiologic evaluation of the central nervous system. ACTH-dependent adrenal hyperplasia can be screened by utilizing morning plasma cortisol levels before and after evening suppression with 1 mg of dexamethasone. High morning levels or poor suppression with dexamethasone indicate the need for further determination of daytime blood levels and free urinary cortisol levels. Hyperpituitarism due to growth hormone and ACTH overproduction is rare, but early recognition is important. Morning sampling for growth hormone and cortisol levels is beset with limitations but nonetheless serves as an important screening technique in the evaluation of persistent hypogonadotropic amenorrhea.

Radiologic enlargement of the sella turcica in association with hypogonadotropism may also occur in patients with the empty sella syndrome,

carotid artery aneurysms, and primary hypothyroidism. Secondary enlargement of the pituitary may develop in primary hypothyroidism, presumably as a compensatory mechanism. The measurement of thyroid-stimulating hormone may help to differentiate sellar enlargement due to primary hypothyroidism from a true intrasellar tumor. The former condition responds readily to thyroid replacement therapy.[25]

Postpartum ischemic infarction and necrosis of the pituitary can occur in association with obstetric shock syndromes (Sheehan's syndrome). This form of hypogonadotropic amenorrhea is usually associated with varying degrees of insufficiency of other pituitary tropic hormones and is manifested clinically by lactation failure, genital atrophy, hair loss, hypotension, hypoglycemia, and anemia. Undetectable serum gonadotropin levels and low T_4, thyroid-stimulating hormone, and plasma cortisol levels corroborate the clinical diagnosis of hypopituitarism due to Sheehan's syndrome.

Drug-Induced Amenorrhea.

Various drugs can induce amenorrhea by virtue of their effect on the hypothalamus or through weight loss secondary to anorexia. Phenothiazine derivatives, reserpine, and ganglion-blocking agents affect the hypothalamus and produce amenorrhea which is sometimes associated with galactorrhea. These effects are usually reversible once the drug is discontinued. Other drugs such as alcohol, digitalis preparations, cytotoxic drugs, and certain antibiotics may produce amenorrhea through their anorectic effect.

The second category of drug-related amenorrhea encompasses oversuppression syndromes following the use of oral or parenteral synthetic steroids. Less than 1% of women taking oral contraceptives develop amenorrhea during or after the use of these agents regardless of the duration of their use. In these women the hypothalamic-pituitary axis is suppressed by the exogenous steroids, and inhibition may persist after the medication is discontinued. This condition of oversuppression may persist for prolonged periods of time. It is important to distinguish amenorrhea secondary to pituitary suppression from "postpill amenorrhea" caused by endometrial involution. In the latter condition, endogenous estrogen levels are normal but the endometrium is unresponsive, possibly owing to the glandular regression induced by the synthetic steroid. Postpill target-organ amenorrhea usually has a good prognosis with spontaneous cure. In "postpill amenorrhea" due to hypothalamic-pituitary oversuppression, most patients spontaneously recover menstrual function within several months. In others, ovulation and consequent pregnancy can be induced by ovulation-inducing drugs. In some instances "postpill amenorrhea" is refractory to all forms of ovulation induction except for human menopausal gonadotropin. Naturally, it is essential to rule out other serious endocrinopathies, e.g., pituitary neoplasia, prior to assuming that amenorrhea is causally related to prior pill use.

Psychogenic Amenorrhea.

Psychogenic stress factors have been recognized as capable of producing amenorrhea. Nevertheless, the precise biochemical intermediaries involved in psychic alterations and gonadotropin production are unknown. The anatomical areas within the limbic system and hypothalamus that affect emotional expression are identical with those which contain steroid receptors and some enzymes involved in steroid metabolism. A hypothesis based upon neuroendocrine control mechanisms suggests that psychic stress may produce a chronic dopaminergic effect with increased neurotransmission and a predominance of dopamine over norepinephrine.

Psychogenic amenorrhea may occur in association with either acute or chronic emotional stress. Psychogenic amenorrhea may also have a strong nutritional component related either to weight loss or weight gain. Neuroendocrine aberrations produced by stress may produce *temporary* or *prolonged* disturbances in gonadotropin and prolactin production. These disturbances producing psychogenic amenorrhea tend to fall into four basic patterns:

Stress-Induced Tonic LH (Short-Term). Temporary interruption of the recycling mechanism may occur as the result of sudden psychic stress. Cyclic LH is replaced by stress-induced, continuous LH production. In most instances failure of the recycling mechanism is brief in duration and there is prompt recovery after 1 or 2 months.

Stress-Induced Tonic LH (Long-Term). If stress factors persist, long-term tonic LH production will produce a clinical picture not unlike polycystic ovarian disease. Amenorrhea will persist and the patient may note mild facial hirsutism with acne. Continued pulsatile LH production will increase ovarian production of Δ^4-androstenedione, testosterone, and estrogen. Vaginal hormonal cytology will reveal many superficial cells, and

bleeding will follow administration of progestational agents. Hyperprolactinemia has been described in some patients with persistent LH elevations, suggesting a condition not unlike pseudocyesis.

Stress-Induced Hypogonadotropism. Eventually, psychic stress may induce loss of both cyclic LH and tonic LH release from the pituitary. This condition may result in low base line levels of FSH and LH. Acquired hypogonadotropism of this type also may occur as the result of nutritional factors, especially weight loss with or without significant psychopathology.

Anorexia may be a symptom of any systemic disease or occur as the result of the use of drugs or medications. The weight loss which occurs secondary to anorexia may produce amenorrhea with low gonadotropin levels. Anorexia in the absence of illness or drug therapy is usually psychogenic in origin. Psychogenic anorexia with weight loss is usually seen before 25 years of age. These individuals have lost at least 25% of their original body weight and exhibit a distorted attitude toward eating and weight gain that over-rides all hunger. They take pleasure in refusing food and losing weight. Such individuals are hyperkinetic with overactivity and have an inappropriate perception of body image. Physical examination may reveal light lanugo hair growth, especially over the back and malar eminences. Bradycardia and low body temperature are present.

Gonadotropin profiles in these patients with weight-loss amenorrhea reveal low LH values and low or normal FSH levels in serum. There is a failure of pulsatile LH output, especially during sleep, and a delayed LH response to gonadotropin-releasing hormone stimulation. The ACTH adrenal axis is altered similarly by decreased pulsatile ACTH and some loss of diurnal variation in plasma cortisol levels. The metabolic clearance rate for cortisol is reduced, apparently in an attempt to maintain internal homeostasis. Elevated serum levels of growth hormone are seen in some of the patients with this type of anorexia. Other findings which have been described include hypercholesterolemia, carotenemia, hypoglycemia, low serum T_3 levels, and increased catechol estrogens.[26, 27] The increased formation of catechol estrogens in these patients is important since they may compete centrally for estrogen binding sites and inhibit the biologic inactivation of catecholamines. Prolongation of catecholamine activity could provide for continued stimulation of dopamine receptors and explain some of the aspects of the anorexia syndrome.[27]

Even in apparent "postpill amenorrhea," the role of weight loss and psychologic factors should receive serious consideration. Women of low body weight, for example, may be at particular risk for developing "postpill amenorrhea."

Stress-Induced Hypogonadotropic Hyperprolactinemia. Some individuals with stress-acquired hypogonadotropism have elevated levels of serum prolactin. The hyperprolactinemia may precede or follow the hypogonadotropism. Pituitary tumors should be the first consideration in hyperprolactinemic patients, but stress-related neuroendocrine dysfunction may produce a comparable pituitary profile.[28] Time and further study should help to delineate the true frequency of stress-induced hyperprolactinemia with amenorrhea.

Psychogenic amenorrhea may be associated with elevated LH levels and low FSH, low LH and normal or slightly elevated FSH, or low gonadotropin/high prolactin profiles. These patterns are usually seen in different patients, but a single individual may pass sequentially through any combination of these different patterns.

Systemic Illness—Endocrine (Excessive or Inadequate Adrenal or Thyroid Function).

Amenorrhea may occur as a result of a systemic endocrinopathy involving an extragonadal endocrine gland. Abnormalities in thyroid function, either hyperthyroidism or hypothyroidism, may produce amenorrhea. Adrenal cortisol overproduction and underproduction may also interfere with normal cyclic gonadotropin production and produce amenorrhea. Thyroid evaluation is an essential part of the diagnostic work-up of amenorrhea, whereas plasma cortisol values are indicated when the clinical picture—including blood pressure and blood sugar—suggest cortisol overproduction.

Systemic Illness—Non-Endocrine.

The precise role of systemic illnesss in the etiology of amenorrhea is not always easy to understand. Generalized systemic illnesses involving poor nutrition, malabsorption syndromes, cardiac disease, renal disease, severe infection, or neoplasia may produce amenorrhea. It is difficult to delineate whether the amenorrhea is directly related to the illness or is the product of psychogenic factors, weight loss, or associated drug therapy. In most systemic disease, anorexia may be largely responsible for the hypogonadotropism. The endocrine abnormalities seen in anorexia nervosa

usually cannot be distinguished from those encountered in starvation due to other causes. Amenorrhea should not be attributed to any systemic illness or psychic disorder until other causes have been eliminated.

Amenorrhea and Galactorrhea.

Amenorrhea and galactorrhea are cardinal symptoms in several syndromes—Chiari-Frommel syndrome, Ahumada-Del Castillo syndrome, and Forbes-Albright syndrome. Although these eponyms have been in common usage, they currently serve very little purpose, and these disorders can be collectively categorized as amenorrhea-galactorrhea syndromes. The development of a sensitive, specific radioimmunoassay for serum prolactin has aided in the identification of those patients with amenorrhea-galactorrhea syndromes who may have prolactin-producing pituitary tumors. All patients with elevation in serum prolactin, regardless of the presence or absence of galactorrhea, should be identified and evaluated for a possible pituitary tumor.

Androgen Excess

The last category of patients with amenorrhea includes those with disorders of androgen overproduction, either adrenal or ovarian. Adrenal androgen overproduction may occur as a result of a virilizing adrenal tumor or congenital adrenal hyperplasia. Virilizing ovarian tumors are rare. The principal cause of ovarian androgen overproduction is the androgenic ovary syndrome, or polycystic ovaries, an etiologically complex and clinically heterogeneous condition. Patients with the polycystic ovary syndrome usually have normal thelarche. Pubarche is followed by sequential growth of hair on the upper lip, chin, intermammary area, and extremities. Serum LH levels are tonically elevated with normal or slight elevations of serum testosterone and urinary 17-ketosteroids. The vaginal smears are remarkably estrogenic, with 25% to 40% superficial cells.

Presumably, this group of hirsute patients with amenorrhea has a constant tonic "leak" of LH which stimulates ovarian production of the weak androgen Δ^4-androstenedione and produces morphologic polycystic ovaries. Increased production rates for testosterone and estrone follow as a result of the increasing formation of the prehormone Δ^4-androstenedione. Increased testosterone production results in hirsutism, while an increased production rate for estrone provides for a well-estrogenized genital tract. Evaluation of patients with androgen overproduction involves principally the measurement of urinary 17-ketosteroids, serum testosterone, and serum LH.[29] In a small number of patients with elevated 17-ketosteroid levels, determinations of urinary pregnanetriol values or plasma 17-hydroxyprogesterone are indicated to rule out "late onset" or "late diagnosed" congenital adrenal hyperplasia.[4]

DIAGNOSTIC APPROACH

General

History

From the previous discussion, it is apparent that historic factors are paramount in evaluating the patient with amenorrhea. Histories of drug ingestion, including oral contraceptives, and psychic stress must receive primary consideration. Careful questioning should be directed toward marked changes in body weight. The psychosocial history should focus on the time span immediately preceding the development of amenorrhea.

Physical Examination

Most patients with amenorrhea have a normal physical appearance. The departures from normal that should receive careful attention include signs of (1) androgen overproduction, (2) cortisol overproduction, (3) galactorrhea, (4) hypothyroidism, (5) acromegaly, (6) weight loss and/or weight gain, (7) short stature—with or without associated somatic anomalies, and (8) sexual infantilism. The last three observations include a careful initial recording of the patient's height, weight, and degree of sexual development. A careful search is made for any somatic anomalies (such as webbed neck) that might additionally suggest ovarian failure associated with a sex chromosome deletion.

Evaluation of Endogenous Estrogen

The pivotal point in the diagnosis of all amenorrhea is an evaluation of the patient's endogenous estrogen production. This can be accomplished clinically by utilizing examinations of the vaginal smear, cervical mucus, or endometrium to bioassay the patient's estrogen capacity. Of these three bioassays, the vaginal smear is probably the most sensitive index, since it exhibits a relatively linear response to increases in endogenous estrogen. Estrogenic quantitation

by endometrial histology is difficult, and endocervical mucus may be limited by the frequent occurrence of endocervicitis. A progesterone challenge test is the most frequently used dynamic test of endogenous estrogen. An appreciation of the scope and limitations of the progesterone challenge is important. The progesterone challenge must be performed with a "pure or C-21" progestin such as progesterone in oil or medroxyprogesterone acetate. The 19-norsteroid compounds are not reagent-pure and may have some intrinsic estrogen contamination, either in their preparation or metabolism. The response to 10 mg of medroxyprogesterone acetate daily for 5 days or to 100 mg of progesterone in oil is a suitable test, but the response must be carefully interpreted to be certain that the withdrawal menses is of sufficient quantity and time span to suggest adequate endogenous estrogen levels. Patients with relatively low levels of endogenous estrogen may occasionally manifest a positive but limited response to a progesterone challenge. Conclusions about endogenous estrogen on the basis of progesterone withdrawal must be guarded in limited response situations. Target-organ failures are best evaluated by prolonged high-dose estrogen challenges. Ultimately, the acquired form of endometrial sclerosis must be diagnosed by hysterography or hysteroscopy. Failure to bleed following estrogen priming does not always indicate the presence of target-organ disease. Long-term hypoestrogenic patients may have a refractory endometrium which requires substantial amounts of estrogen priming before displaying a positive response. This is especially true in the weight-loss hypoestrogenic amenorrheas. Overproduction of catechol estrogens in these patients may have an anti-uterotropic effect.[27]

The measurement of peripheral estrogenic steroids has a very small practical role in the quantitation of endogenous estrogen. The intermediary metabolism of estrogens is extremely complex. The interpretation of a single measurement of the blood level of a specific estrogen is difficult and of limited value in patient management. Normal or low estrogen values are difficult to interpret, but unusually high serum values for total estrogen or estradiol may be helpful in suggesting an estrogen-producing ovarian tumor. The clinician is best served by using the bioassay principle as exemplified by the vaginal smear or the progesterone challenge test. In certain situations, indirect quantitation of peripheral estrogen can be obtained by measuring serum levels of the appropriate feedback hormone, namely FSH. In unusual patients the target-organ effects of estrogen may be normal but serum FSH levels are markedly elevated. These unusual patients are categorized as having euestrogenic forms of ovarian failure.[30] They serve to emphasize the differential sensitivity to estrogen of target tissues, including the hypothalamus. Differential target-organ sensitivity and limitations of the estrogen assay point out the need to measure serum FSH in clinically suspected hypoestrogenism.

Specific

The evaluation of any patient will depend upon the assessment of endogenous estrogen. On the basis of the vaginal smear or progesterone challenge, patients with amenorrhea can be separated prognostically into those with normal and low endogenous estrogen levels. The prognosis for spontaneous cure is good in the normal group and guarded in the hypoestrogenic category. Any diagnostic work-up for amenorrhea should be prefaced by a concern for the "target-organ pathology" of pregnancy. A β-subunit assay for human chorionic gonadotropin should be obtained if there is any suspicion of active, viable, trophoblastic tissue.

The diagnostic work-up of amenorrhea, categorized on the basis of endogenous estrogen levels, is outlined in Table 3. The sequential work-up of each group is designed to uncover the most frequent and serious etiologies associated with normal or low estrogen production. Etiologic overlap occurs frequently, since temporary euestrogenism is a transitional stage for severe forms of hyper- and hypogonadotropism.

Low-Estrogen Group

Patients with low endogenous estrogen levels must be evaluated for central nervous system disease or for hypergonadotropic forms of ovarian failure. The initial evaluation includes skull x-rays and measurement of serum levels of T_4, T_3, and gonadotropins. Plasma cortisol levels are obtained if the clinical phenotype suggests cortisol overproduction or if the blood pressure or blood sugar is elevated. The measurement of serum gonadotropins, specifically FSH, is necessary in all hypoestrogenic patients. If serum gonadotropin levels indicate hypergonadotropism, then cytogenetic studies should be performed on all patients, especially short-statured individuals (below 63 inches in height).[4] If serum gonadotropin levels are low, one should pause temporarily in

TABLE 3. *Schematic Outline of the Diagnostic Evaluation of Amenorrhea*

Initial step: rule out presence of trophoblast (β-subunit human chorionic gonadotropin)	
Low	Normal
Consider principally central nervous system Skull: lateral, posteroanterior films T_4, T_3, blood sugar, plasma cortisol determinations FSH/LH High: cytogenetic studies Low: intensive psychosocial evaluation Before proceeding further, expand psychosocial history; then Serum prolactin, 17-ketosteroid determinations Growth hormone determinations, tomograms, visual field examination, CAT scan	Consider principally temporary failure of recycling Skull: lateral, posteroanterior films T_4, T_3, blood sugar, plasma cortisol determinations Before proceeding further, give alternate-month therapy; then Serum LH/testosterone determinations 17-Ketosteroid determinations Endometrial biopsy if vaginal smear reveals 40% or more superficial cells

the diagnostic work-up and intensify the psychosocial-nutritional history. The frequency of psychogenic amenorrhea warrants this expense of time before embarking on further sophisticated endocrine and central nervous system evaluation.

The majority of patients with acquired monotropic failure of gonadotropins will be found to have psychogenic amenorrhea or amenorrhea related to weight loss. If hypogonadotropism persists, then serum prolactin levels must be obtained to identify the "silent hyperprolactinemic" individuals who are suspect for prolactin-producing pituitary tumors. The measurement of 17-ketosteroids in urine may be indicated in rare patients with hypogonadotropism in order to identify androgen overproduction in the absence of hirsutism. The latter may occasionally be important in the diagnosis of rare adrenal tumors when clinical evidence of androgen overproduction is limited. If hypogonadotropic hyperprolactinemia persists, then growth hormone levels at rest and after 30 minutes of exercise should be obtained. Further endocrine evaluation should be combined with visual field studies and polytomography of the sella turcica. The combination of tomographic abnormalities, persistently low gonadotropin levels, elevated serum prolactin levels, and blunted growth hormone responses to provocation testing suggests a central nervous system lesion. Decisions for further invasive studies of the central nervous system are individualized on the basis of this information and the clinical course of the patient's illness.

Normal-Estrogen Group

The vast majority of patients with normal endogenous estrogen is composed of patients who experience temporary interruptions of the recycling mechanism with tonic elevation of LH. In some instances the tonic LH elevation may persist with resultant ovarian overproduction of androgens. A few patients in the normal-estrogen group may have acquired target-organ disease due to endometrial sclerosis. The evaluation of the euestrogenic amenorrheic patient is provided in Table 3. Although endogenous estrogen levels in this group are normal, screening of the central nervous system should be performed in order to eliminate patients who may have early pituitary tumors. Evaluation for hypothyroidism is still necessary since hypothyroid patients may be euestrogenic.

Plasma cortisol levels are obtained in the presence of clinical evidence of hypercortisolism. Interference with ovarian estrogen production may be a late finding in some disorders with cortisol excess. If skull x-rays and thyroid evaluation are normal, a pause in the evaluation is justified while a pure progestin or C-21 compound is administered on a cyclic basis. A synthetic progestin such as medroxyprogesterone acetate, 10 mg daily, can be administered for the first 5 days every other month over a 6-month time span. One should be reasonably certain from the appearance of the vaginal smear that withdrawal bleeding will occur. Failure to bleed after the medication may generate further anxiety and concern on the part of the patient, if not adequately prepared. Withdrawal menses following the administration of medroxyprogesterone acetate in alternate months serves to relieve anxiety, confirms that endogenous estrogen is adequate, and indicates a patent, responsive genital tract. During the alternate months in which medroxyprogesterone acetate is not given, spontaneous menses may occur. The vast majority of patients who have temporary interruption of the recycling mechanism will usually experience spontaneous menses during or following the alternating 6-month trial of a pure progestin.

If there is clinical evidence of androgen overproduction, then serum LH, serum testosterone,

and urinary 17-ketosteroids should be studied. In some patients with androgen overproduction, the vaginal smear exhibits more than 40% superficial cells. Endometrial biopsy should be performed to rule out undue degrees of endometrial hyperplasia. Endometrial biopsy and uterine sounding are also indicated in those patients who have adequate estrogen effect as judged by the vaginal smear but who do not bleed after a progesterone challenge. These include patients who may have acquired forms of endometrial sclerosis (Asherman's syndrome) or a missed abortion with residual hyalinized villi.

SUMMARY

Amenorrhea is a ubiquitous problem, and clearly tangible causes are evident only in a relatively small number of patients. The clinician should proceed cautiously and select appropriate laboratory studies which will be of maximal benefit to the patient. While the evaluation of endogenous estrogen, skull x-rays, and serum gonadotropin levels are in progress, a continued dialogue with the patient must continue in order to identify factors that may contribute to psychogenic amenorrhea. Continued studies in the area of neuroendocrinology may help to clarify the relationship between the functions of the neocortex and gonadotropin production. Advancements in this area should help the clinician in his attempts to separate dysfunction from organic pathology. Meanwhile, the approach to amenorrhea should be tempered by a constant vigilance for pituitary tumors. The physician must always be aware of the role of psychosocial and nutritional factors in the interruption of the cyclic mechanism.

REFERENCES

1. Marshall WA, Turner JM: Variations in pattern of pubertal changes in girls. Arch Dis Child 44:291, 1969
2. Ross GT, Cargille CM, Lipsett MB, Rayford PD, Marshall JR, Strott CA, Rodbard D: Pituitary and gonadal hormones in women during spontaneous and induced ovulatory cycles. Recent Prog Horm Res 26:1, 1970
3. Griffin JE, Edwards C, Madden JD, Haxzod MJ, Wilson JD: Congenital absence of the vagina. The Mayer-Rokitansky-Kuster-Hauser syndrome. Ann Intern Med 85:224, 1976
4. McDonough PG: Menarchal delay. In Current Problems in Obstetrics and Gynecology, Edited by RW Kistner. Chicago, Year Book Medical Publishers, 1977, p 1
5. Lischke JD, Curtis CH, Lamb EJ: Discordance of vaginal agenesis in monozygotic twins. Obstet Gynecol 41:920, 1973
6. Asherman JG: Amenorrhea traumatica (atretica). J Obstet Gynaecol Br Emp 55:23, 1948
7. Akinkugbe A: Vaginal atresia and cryptomenorrhea. Obstet Gynecol 46:317, 1975
8. McDonough PG, Byrd JR, Tho PT: Phenotypic and cytogenetic findings in 82 patients with primary ovarian failure—changing trends. Fertil Steril 28:638, 1977
9. Saenger P, Levine LS, Wachtel SC, Korth-Schutz S, Doberne Y, Koss GC, Lavengood RW Jr, German JL III, New MI: Presence of H-Y antigen and testis in 46,XX true hermaphroditism, evidence for Y chromosomal function. J Clin Endocrinol Metab 43:1234, 1976
10. McDonough PG, Greenblatt RB, Byrd JR, Hastings EV: Gonadoblastoma (gonocytoma III): report of a case. Obstet Gynecol 29:43, 1967
11. McDonough PG: Primary ovarian failure. In Endocrine Causes of Menstrual Disorders: Proceedings of the Second Annual Symposium on Gynecologic Endocrinology, Edited by J Givens. Chicago, Year Book Medical Publishers, 1978
12. McDonough PG, Byrd JR: Gonadal dysgenesis. Clin Obstet Gynecol 20:565, 1977
13. Espiner EA, Veale AM, Sands VE, Fitzgerald PH: Familial syndrome of streak gonads and normal male karyotypes in five phenotypic females. N Engl J Med 283:6, 1970
14. Swyer GIM: Male pseudohermaphroditism: a hitherto undescribed form. Br Med J 2:709, 1955
15. Greenblatt RB, Byrd JR, McDonough PG, Mahesh VB: The spectrum of gonadal dysgenesis. Am J Obstet Gynecol 47:351, 1967
16. McDonough PG, Tho PT, Byrd JR: Twins discordant for 46,XX gonadal dysgenesis. Fertil Steril 28:251, 1977
17. Cohen MM, Capraro VJ: Pericentric inversion of a group D chromosome (13-15) associated with amenorrhea and gonadal dysgenesis. Am Hum Genet 30:313, 1967
18. Kleerekoper M, Bastan H, Penny R, Posen S: Idiopathic hypoparathyroidism with primary ovarian failure. Arch Intern Med 134:944, 1974
19. Jones GS, Moraes-Rhuehsen MD: A new syndrome of amenorrhea in association with hypergonadotropism and apparently normal ovarian follicular apparatus. Am J Obstet Gynecol 104:597, 1969
20. Koninckx PR, Brosens IA: The "gonadotropin-resistant ovary" syndrome as a cause of secondary amenorrhea and infertility. Fertil Steril 28:926, 1977
21. DeLange WE, Weeke A, Artz W, Jansen W, Dorenbos H: Primary amenorrhea with hypertension due to 17-hydroxylase deficiency. Acta Med Scand 193:565, 1973
22. McDonough PG, Mahesh VB, Byrd JR: The diagnostic use of gonadotropins. Fertil Steril 2:126, 1970
23. Boyar RM, Wu RHK, Kapen S, Hellman L, Weitzman ED, Finkelstein JW: Clinical and laboratory heterogeneity in idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 43:1268, 1976
24. Kulin HE, Santner SJ: Timed urinary gonadotropin measurements in normal infants, children and in patients with disorders of sexual maturation. J Pediatr 90:760, 1977
25. Keye WR, Ho Yuen B, Knopf RF, Jaffee RB: Amenorrhea, hyperprolactinemia and pituitary enlargement secondary to primary hypothyroidism. Obstet Gynecol 48:697, 1976
26. Warren MP, Vande Wiele RL: Clinical and metabolic features of anorexia nervosa. Am J Obstet Gynecol 117:435, 1973

27. Fishman J, Boyar RM, Hellman L: Influence of body weight on estradiol metabolism in young women. J Clin Endocrinol Metab 41:989, 1975
28. Zacur H, Chapanis WP, Lake CR, Ziegler M, Tyson JE: Galactorrhea-amenorrhea: psychological interaction with neuroendocrine function. Am J Obstet Gynecol 125:850, 1976
29. Yen SCC, Vela P: Inappropriate secretion of FSH and LH in polycystic ovarian disease. J Clin Endocrinol Metab 30:435, 1970
30. Falk RJ: Euestrogenic ovarian failure. Fertil Steril 28:502, 1977