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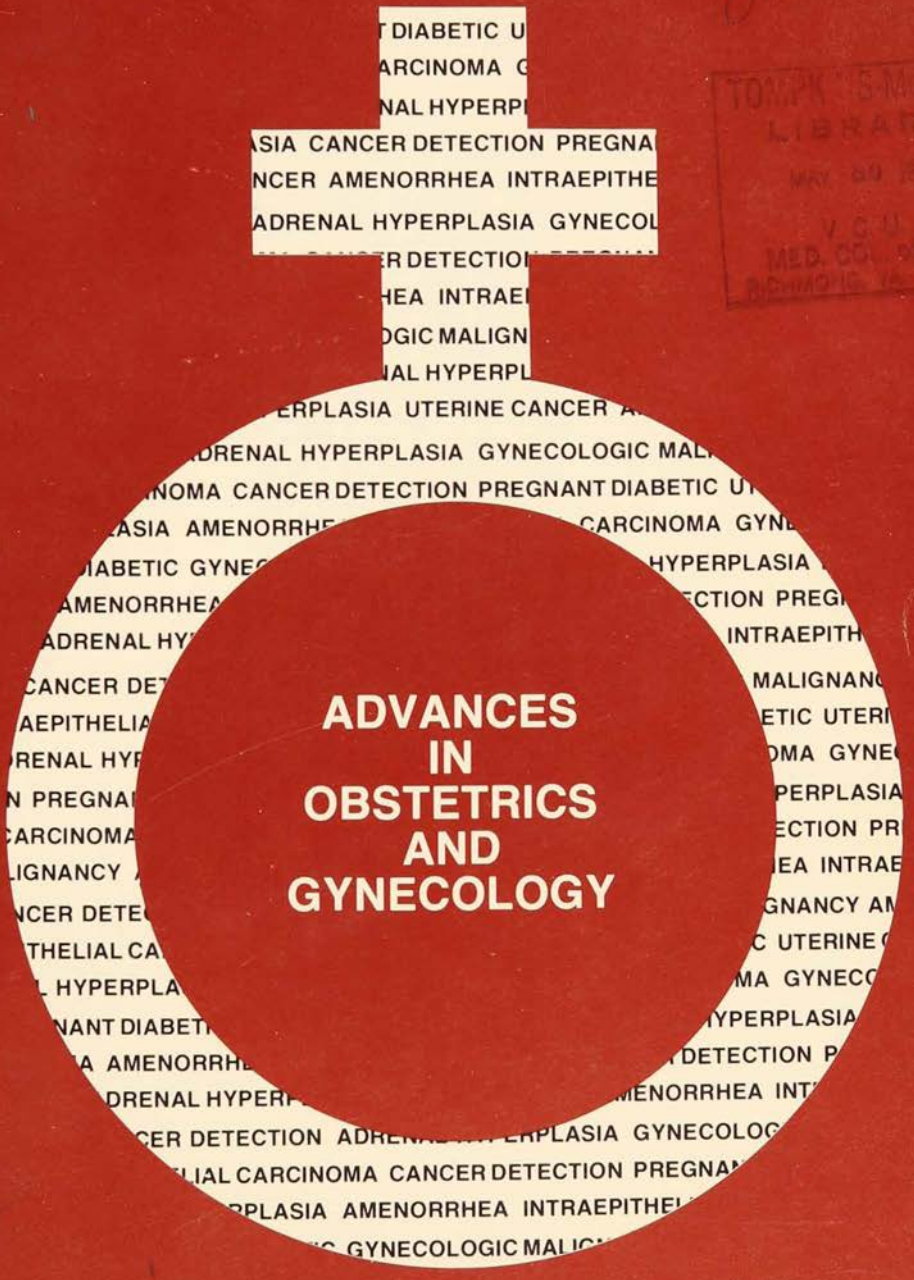
MEDICAL COLLEGE OF VIRGINIA QUARTERLY
VOLUME ELEVEN • NUMBER ONE • 1975



ADVANCES IN OBSTETRICS AND GYNECOLOGY

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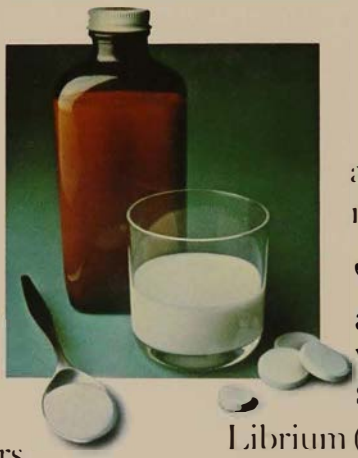

Excessive anxiety in susceptible patients can set in motion a chain of responses, the end results of which may be gastric hypersecretion and intestinal hypermotility; such processes may aggravate organic gastrointestinal disorders and impair the effectiveness of medical management. Furthermore, intense anxiety can interfere with patient cooperation in following your therapeutic directives. When counseling and reassurance alone are inadequate to relieve undue anxiety, adjunctive Librium may be beneficial.

"Specific" for anxiety reduction... wide margin of safety

Librium (chlordiazepoxide HCl) is used as an adjunct to primary gastrointestinal medications since it acts directly on the central nervous system reducing excessive anxiety and emotional tension. In so doing, Librium indirectly affects gastrointestinal function.

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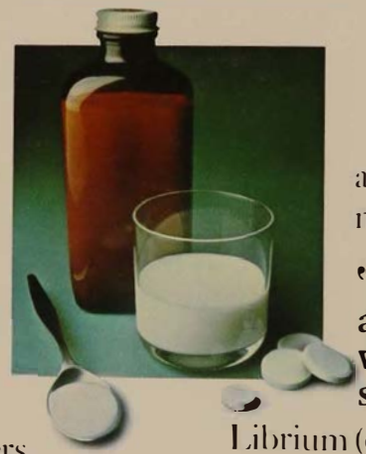

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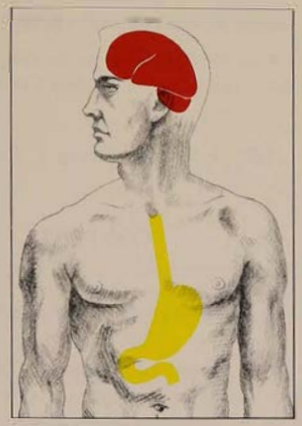

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Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

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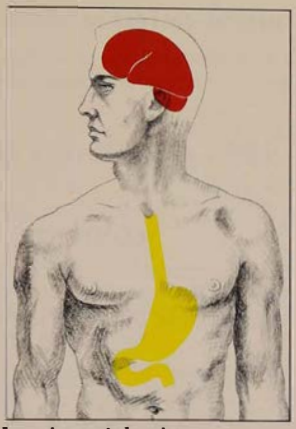

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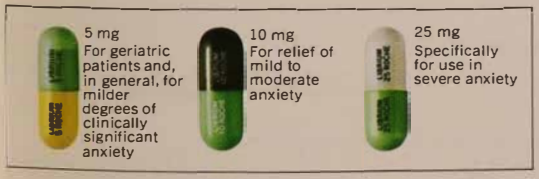

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A Scientific Publication of the School of Medicine
Health Sciences Division of Virginia Commonwealth University

1975 • Volume Eleven • Number One

MEDICAL COLLEGE OF VIRGINIA QUARTERLY Published quarterly (Spring, Summer, Fall, Winter), by the Medical College of Virginia, Division of Health Sciences, Virginia Commonwealth University. The QUARTERLY publishes results of original research in basic and clinical sciences. Contributions from outside the Medical College of Virginia faculty are invited. Manuscripts, submitted in duplicate, should be prepared according to recommendations in the Style Manual for Biological Journals, Washington, D.C., American Institute of Biological Sciences, Second Edition, 1964.

Correspondence: MEDICAL COLLEGE OF VIRGINIA QUARTERLY, Medical College of Virginia, Richmond, Virginia 23298. Phone 804/770-4027.

Subscription rates for U.S.A., Canada, and Mexico: 1 year, $6.00; 2 years, $10.00; 3 years, $14.00. All other countries: 1 year, $8.00; 2 years, $12.00; 3 years, $15.00. Libraries and institutions: (*U.S.A.*) 1 year, $12.00; 2 years, $20.00; 3 years, $28.00; (*foreign*) 1 year, $13.00; 2 years, $21.00; 3 years, $29.00. Interns, residents, and students: 1 year, $3.00. Single issue: $2.00.

Third class postage paid at Richmond, Virginia.

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THE 46TH ANNUAL MCGUIRE LECTURE SERIES
Advances in Obstetrics and Gynecology

Sponsored by the School of Medicine, Department of Continuing Education and the Department of Obstetrics and Gynecology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, and the H. Hudnall Ware, Jr. Society.

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Printed by the William Byrd Press, Richmond, Virginia

INTRODUCTION

Few areas in medicine can equal the rapid proliferation of information that has occurred and continues to occur in the area of human reproduction. The progress in our understanding of the underlying mechanisms which control the human female reproductive system has led to an ever-increasing refinement in the definition of pathologic states and the development of specific, effective therapeutic agents for some of these. It is clear that not all is yet known and that there is need for repetitive reassessment of our knowledge in order to keep abreast of these rapid discoveries. Pregnancy, once achieved, is subject to yet another system of hazards about which a great deal has been learned. Both maternal and fetal diseases have become better understood through more refined diagnostic methods. More specific and successful methods of management have been designed. The improvement in the outcome of these high-risk pregnancies can now be demonstrated, but it does require up-to-date knowledge and skills on the part of the physician and a constant effort against the social and economic obstacles which prevent optimal care. With the occurrence of malignant change in the reproductive organs, a new set of hazards is experienced. The admirable degree of international cooperation among gynecologic oncologists with common staging systems and controlled therapeutic studies has led to rapid improvement in cure rates of most, but not all, gynecologic malignancies. Periodic review of present therapeutic modalities, newer (and generally more conservative) modalities, and the accumulated epidemiologic data is of importance in keeping us oriented. Understanding of gynecologic malignancies has contributed much to our understanding of many similar malignancies.

Not all the changes which are occurring can be reviewed within the scope of this conference. However, we are indeed fortunate to be able to learn the most current information from recognized leaders in their specific field. We are most grateful to our guest lecturers who interrupted their busy and productive lives to come to Richmond to share their knowledge with us and to our MCV faculty for their participation.

Our special thanks to Dr. Saul B. Gusberg who was the 46th McGuire Lecturer and to Dr. Robert A. Munsick, our second H. Hudnall Ware, Jr. Visiting Professor. We would also like to recognize the H. Hudnall Ware, Jr. Society and its president, Dr. Louis Keffer, for their sponsorship and participation.

LEO J. DUNN, M.D.

Professor and Chairman
Department of Obstetrics and Gynecology
Medical College of Virginia
Virginia Commonwealth University

Modern Management of Diabetic Pregnancies*

ELSIE R. CARRINGTON, M.D.

Professor and Chairman, Department of Obstetrics and Gynecology, Medical College of Pennsylvania, Philadelphia, Pennsylvania

On a broad national basis, it should be quite possible to substantially reduce maternal morbidity and the disproportionately high numbers of perinatal losses associated with diabetic pregnancies. Nationwide, the overall perinatal mortality rate for this group is approximately 20%, which is at least double that incurred in centers where intensive care facilities and personnel are available, and consistent, well-coordinated care by the health team is provided.

Although the prognosis for fetal survival is less favorable with advances in severity of the diabetic state, there is a significant risk even during the mildest stage of the disease. Careful prospective studies, notably those of O'Sullivan and his group, have demonstrated that gestational diabetics have a higher than normal perinatal mortality. Prevention begins with diagnosis.

Detection. Ideally, a two-hour postprandial screening of blood sugar following a 100 g carbohydrate-equivalent breakfast should be a standard prenatal laboratory test. In practicality, all patients with a poor obstetric history, previous perinatal losses, large babies, a family history of diabetes, glycosuria, or significant obesity are candidates for a glucose tolerance test. Using these criteria, we subjected 3,340 prenatal patients to the three-hour glucose tolerance test following a 100 g glucose load, and 540 showed abnormal responses. The yield of positives, therefore, was 1 in 6.3 suspects, and the overall incidence of gestational diabetes in this Philadelphia population was 1.18%. Criteria used are as follows: fasting = 90 mg %; 1 hour = 165 mg %; 2 hour = 145 mg %; 3 hour = 125 mg %. Glucose tolerance is impaired if two or more of these values are equaled or exceeded. The test is performed on whole blood using the Somogyi method or autoanalyzer (Hoffman) method. If plasma or serum is used, 10 mg % should be added to each of the values. The importance of a very large screening program was shown in the prospective study conducted by O'Sullivan and his group who found that screening is particularly important in the obese, older-age patient. Perinatal mortality was 1.5% for normal control patients and 6.4% for those with gestational diabetes. The increase in perinatal loss was strikingly evident in gestational diabetic mothers 25 years of age or older, with the risk further increased by obesity.

Metabolic Control. How strict should this be? These patients are ketosis prone. Ketosis is one of the most lethal events for the fetus, but one of the most preventable complications for the mother. The incidence of intrauterine fetal death is greatly increased in pregnancies complicated by pre-coma maternal acidosis. Of further concern is the fact that the National Collaborative Study reveals a significant relationship between maternal ketonuria and central nervous system defects or deficiencies in the offspring. Neither insulin treatment nor hypoglycemia shows a positive association. For these reasons the patient should be kept as nearly normoglycemic as possible and free of ketonuria even at the expense of an occasional episode of hypoglycemia which is readily controlled.

Many, but not all, gestational diabetics can be maintained on diet alone. The response to diet is determined on the basis of a two-hour postprandial blood sugar obtained at two-week intervals. If the

* The following summarizes the main points of a lecture presented by Dr. Carrington at the 46th Annual McGuire Lecture Series, December 5, 1974, at the Medical College of Virginia, Richmond.

two-hour value on diet cannot be maintained below 160 mg %, the patient needs insulin, and for the purpose of management of the pregnancy such patients should be considered in the insulin-dependent category.

Is there any advantage in treating all gestational diabetics with low-dose insulin? Several groups in this country and abroad have compared treated and untreated cases. Apart from slight reduction in oversized infants, other advantages are not yet sufficiently clear-cut to warrant recommending this approach. Oral hypoglycemic agents should not be used in pregnancy. In contrast to insulin, the sulfonyl ureas pass the placental barrier readily. Neonatal hepatic function is relatively immature, and the newborn metabolizes these drugs poorly. Intractable hypoglycemia persisting as long as the eleventh day of life, and in some instances requiring exchange transfusion, have been reported, particularly in relation to long-acting preparations such as chlorpropamide. The biguanides which raise the blood lactate level may accentuate the tendency to maternal ketoacidosis and are contraindicated during pregnancy.

The anti-insulin effects of pregnancy usually cause significant changes in insulin needs after the 20th week of gestation. The rise in requirement is sometimes precipitous about the 24th to 26th week. Both the patient and the physician should be on the lookout for these changes. In our patients, 75% needed a mean of about 60% more insulin. Twenty-three percent showed only minor increase in insulin requirement. Only an occasional patient showed reduction in insulin need.

One of the poorly understood problems has to do with remission, which may occur particularly in the early stages of diabetes. How does one handle the patient who states that she had an abnormal glucose tolerance test with her previous pregnancy and was treated accordingly, but the glucose tolerance test in the present pregnancy is normal? While it is the rule that the diabetic state will progress, remissions do occur. We have encountered this phenomenon in a number of gestational diabetics and in one case of juvenile diabetes. Since the adverse effect upon the fetus can occur at any stage including the prediabetic period, it is important to accept the reality of remission and to avoid the temptation to ascribe its occurrence to faulty initial diagnosis.

Most diabetics have some degree of hydramnios, excessive in approximately 10% of cases. The common practice of prophylactic use of diuretic and rigid salt restriction may do more harm than good. Thiazides are useful only in otherwise uncomplicated fluid retention. If administered alternately three days on and three days off, these drugs will often reverse simple fluid shifts without disturbing electrolyte balance, but they are ineffectual for reversal of toxemia or hydramnios. Hospitalization is necessary if these conditions develop. Asymptomatic bacteriuria is found in about 12 or 13% of diabetic pregnancies, or approximately twice the overall incidence, and should be treated when found.

Prenatal Monitoring. The ability to predict intrauterine fetal deaths in diabetic pregnancies on clinical evidence alone has limitations. A reliable method for assessing intrauterine fetal welfare should be available in every diabetic pregnancy. Although no single test is capable of detecting all types of malfunctions that affect the fetus, the urine estriol test is, in our experience, indispensable. The fact that estriol production requires a fetal as well as a placental component is an obvious advantage. The types of cases in which estriol values may be misleading are small in number and can usually be readily identified. These are mainly cases in which renal function is markedly reduced and renal clearance of estriol diminished.

Although the majority of patients with mild diabetes can be maintained free of complications and await labor at term, some cannot. Fetal deaths do occur in the virtually asymptomatic, well-controlled gestational diabetic pregnancy. In these cases, estriol determinations have proved to be of great value in identifying the fetus in jeopardy who should be delivered and, on the other hand, in providing reassurance and safe conduct through the natural course of pregnancy when estriol values remain in the normal range.

Recent recommendations have been made to apply the same principles to pregnancies complicated by overt diabetes. While it is feasible to individualize and extend the timing of delivery to the 38th week or even beyond in many cases of B and C insulin-dependent diabetics, those with advanced disease are poor candidates for this approach, even with frequent monitoring. From a practical point of view, and purely on clinical grounds, pregnancy in a patient with angiopathy, retinopathy, or nephropathy can rarely be carried beyond the 37th week, and all too often the pregnancy has to be terminated before that

optimal time in the interest of the mother or baby or both. The suddenness with which serious changes or events can take place in these patients and the fact that methods for determining fetal maturity are available (particularly the lecithin/sphingomyelin ratio and the creatinine concentration) offset the possible advantages of attempting to extend the gestational period for Classes D, E, and F diabetics beyond 37 weeks.

The infant of a diabetic mother is at risk from the moment of birth. Respiratory distress is the greatest threat. It is most directly related to prematurity and accentuated in diabetes. While tests for fetal maturity should make iatrogenic prematurity preventable, early delivery will continue to be necessary in selected cases to avoid intrauterine fetal death or damage. The neonatologist experienced in dealing with respiratory pathophysiology who can initiate treatment within minutes after birth, and a neonatal intensive care unit capable of providing clinical and laboratory support services on a 24-hour-a-day basis offer the best chance for intact survival.

In principle, the problems of diabetic pregnancies do not differ from the problems of at least two-thirds of all high-risk pregnancies, and in this respect, they serve as a prototype for centralized perinatal care. The demands in terms of medical and paramedical manpower, the high cost of services and facilities comprising the perinatal center, and the concern for quality of life will surely require revision of the current health care delivery system. Consolidation of scarce resources in centers, whether teaching or community hospitals, capable of providing specialized care for the high-risk mother and newborn is the logical approach.

The Endocrinologic Evaluation of Amenorrhea* **

CHARLES B. HAMMOND, M.D., R. HERBERT WIEBE, M.D.,
LEE TYREY, PH.D., DAVID W. SCHOMBERG, PH.D.

Division of Endocrinology and Infertility, Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, North Carolina

Introduction. The purpose of this paper is to review the endocrinologic evaluation of 58 patients who presented to our institution this past year with a chief complaint of absent or irregular menses. The primary goal for presenting these patients is to review the results of several newer studies as well as older and more classical studies which are useful in the differential diagnosis of amenorrhea. Such newer studies not only take advantage of the more current knowledge of the ovulatory process but also utilize recently developed and highly sensitive techniques of hormonal assay. It is hoped that this will provide the reader with some suggestions for a current and efficient method to evaluate the several causes of amenorrhea.

Materials and Methods. Amenorrhea is usually categorized as being either primary or secondary, and the patient's age or duration of absent menses varies among the several definitions available. For the purpose of this paper the following definitions will be utilized:

Primary Amenorrhea. Failure to have initiated menstrual bleeding by age 18.

Secondary Amenorrhea. Cessation of previously established menses for an interval of more than one year.

Oligomenorrhea. Spontaneous, irregular menses occurring at intervals of not less than three months.

Fifty-eight patients were studied and were divided into three major diagnostic categories according to their presenting menstrual patterns. Eight patients had *primary amenorrhea,* forty-six had *secondary amenorrhea,* and four patients had *oligomenorrhea.* Other patients with demonstrable uterine causes of amenorrhea are excluded from this study. This included patients with Asherman's syndrome, müllerian abnormalities in which no uterus was present, and testicular-feminization patients. Thus, all patients included had uteri capable of normal menstruation, and this was evidenced by progesterone-induced withdrawal bleeding, endometrial biopsy, estrogen-progesterone withdrawal bleeding, and/or hysterosalpingogram. Patients with easily diagnosable abnormalities of thyroid or adrenal function also are not included, as early outpatient studies usually revealed the etiology of their amenorrhea and appropriate therapy resulted in prompt return of menstrual function. For these reasons one can not draw valid incidence frequencies from this referral-practice population of 58 amenorrheic patients.

Studies Performed. All 58 patients were hospitalized on the Clinical Research Ward of our institution and underwent study. Tests included a thorough general and endocrine history, complete physical and pelvic examination, Papanicolaou smear, vaginal cytologic maturation index, complete blood count, urinalysis, Chem-18, anteroposterior (AP) and lateral skull x-rays, chest x-ray, and visual fields by perimeter.

All 58 patients also underwent a series of

* Presented by Dr. Hammond at the 46th Annual McGuire Lecture Series, December 5, 1974, at the Medical College of Virginia, Richmond.

** Supported by a grant (RR-30) from the General Clinical Research Centers Program of the Division of Research Resources, National Institute of Health.

baseline and dynamic hormonal testing. Serum total estrogen (1), progesterone (2), follicle stimulating hormone (FSH) (3), luteinizing hormone (LH) (4), and growth hormone (5) were all performed in duplicate by standard radioimmunoassay techniques. Serum prolactin was initially done in the laboratory of Dr. Henry Friesen and later by Dr. Stuart Handwerger, both using radioimmunoassay (6). Serum T_4 and T_3 Uptake were done by standard techniques, as were urinary 17-hydroxycorticoids and 17-ketosteroids.

All patients also underwent the following three dynamic tests of pituitary function:

1. Hypoglycemia was induced by the intravenous administration of 0.1 units insulin per kilogram with blood glucose and human growth hormone (radioimmunoassay) determined at intervals over 90 minutes. Blood glucose had to achieve at least 50% reduction from fasting levels to be considered an adequate stimulus for the release of growth hormone. A positive growth hormone response to insulin-induced hypoglycemia consisted of a peak value of growth hormone greater than 10 ng/ml (7).

2. Control 24-hour urine collections were obtained for 17-hydroxycorticoids (17OH) and 17-ketosteroids (17KS). If normal hydroxycorticoids were present, the patient was then given Metopirone®, 750 mg orally every 4 hours for 6 doses. After the last dose of Metopirone®, another 24-hour urine collection was made. A normal response of pituitary ACTH was considered present if the levels of 17-hydroxycorticoids doubled (8).

3. The ability to release gonadotropins was tested with LH-FSH Releasing Hormone. Baseline FSH and LH were determined, then the patients received 100 μg SC of AY 24031, Ayerst Laboratories LH-FSH Releasing Hormone. Blood samples were then taken at frequent intervals over a period of 6 hours, and duplicate samples were assayed by radioimmunoassay for FSH and LH. Serum total estrogens were determined by radioimmunoassay on the control and 6-hours samples. Currently we are evaluating a variety of response parameters, and we realize that our own criteria for a positive response may be altered. However, in the interim, a positive response to LH-FSH Releasing Hormone was considered present if *both* serum LH rose by more than fourfold over baseline and serum FSH at least doubled (9).

Other Studies. As patients were evaluated by the techniques listed previously, many were found to have significant abnormalities which required further investigation. Such studies included:

Patients with *prolactin excess* (on duplicate samples) usually underwent further testing of prolactin kinetics with L-dopa, chlorpromazine, water load, and other studies. If the excess secretion was not readily explainable, then sella turcica tomography and pneumoencephalography were usually performed.

Evidence of clinical *androgen excess* or significant laboratory documentation of this usually led to determination of serum testosterone, urinary pregnanetriol, and appropriate dexamethasone suppression. If an ovarian source was presumed, then laparoscopy and ovarian biopsy were carried out.

Elevated 17-hydroxycorticoids led to the determination of plasma cortisol and dexamethasone suppression, with pituitary evaluation if pituitary tumor was suspected.

Abnormal *thyroid function* was evaluated by traditional methodology.

Patients who had stigmata of gonadal dysgenesis, or primary amenorrhea which seemed of gonadal origin (such as evidenced by elevated gonadotropins), were then evaluated by buccal smear and karyotype of peripheral leukocytes. If there was evidence of significant early estrogen production or a "Y" chromosome on karyotype, then laparoscopy and gonadal biopsy with both histopathologic study and gonadal karyotype were done. Gonads with "Y" chromosome were surgically removed.

If patients had abnormal skull x-rays or significant endocrinologic evidence of hypopituitarism or pituitary tumor, then tomograms of the sella turcica, pneumoencephalography, and/or carotid arteriography were performed.

Once a diagnosis was achieved, appropriate therapy was carried out. No patient suffered any significant side effects from any of these diagnostic studies.

Results. After these 58 patients had completed the previously listed diagnostic studies, a final diagnosis was assigned. The tables which follow (Tables 1, 2, 3) are each arranged with patients grouped by these final diagnoses and the results of the various diagnostic tests listed below. In this fashion one can not only study the results of the several tests performed in patients with a particular cause of amenorrhea but also evaluate how a specific test may provide useful data in the several groups of patient diagnoses.

TABLE 1
Primary Amenorrhea
(8 Patients)

Diagnosis (No.)	Constitutional Delay (3)	Hypothalamic Cause (2)	?Congenital Absence LH (2)	Gonadal Dysgenesis (1)
Family Hx.	+	–	–	–
Estrogen	↓	↓ sl.	↓	↓
FSH-LH	FSH-Normal LH-sl. ↑	FSH-Normal LH-sl. ↑	FSH-Normal LH-sl. ↓	↑↑
HGH, Prolactin, 17OH, 17KS, Thyroid	–	–	–	–
LRH Test	FSH + LH +	FSH + LH +	FSH + LH –	FSH + LH +
Insulin-HGH	+	+	+	+
Metopirone*	+	+	+	+

+ positive response, or normal test result.
– negative response, or reduced test result.
(See text for details.)

Primary Amenorrhea (Table 1). Eight patients presented with primary amenorrhea. Three patients were felt to have constitutional delay of menarche. Family history was positive in all three patients, and, while all had had a sequential development of secondary sex characteristics, all had reduced estrogen levels. Levels of FSH were normal and LH levels were minimally elevated in all three patients. Baseline testing of other hormones was normal. There was a significant response in all patients to LH Releasing Hormone, Insulin-Growth Hormone, and Metopirone®. The patients' ages were 18, 19, and 23 years. All have subsequently begun spontaneous menses.

Similar findings to those mentioned in the previous category were present in the testing of two patients thought to have "hypothalamic" primary amenorrhea, except there was no family history of delayed menarche.

Two patients had low baseline serum LH and failed to elevate LH in response to LH-Releasing Hormone on either of two occasions. This suggested to us a reduced ability to produce, or release, or a congenital diminution in LH.

Finally, one patient had Turner's syndrome (gonadal dysgenesis) which was proven by karyotype. Serum FSH was quite high, but there still existed a capacity of the pituitary to increase gonadotropin release when LH-Releasing Hormone was given.

Secondary Amenorrhea-Organic (Table 2). Sixteen patients presented with secondary amenorrhea which was finally shown to be of an organic etiology.

Four patients had pituitary tumors; one, a patient with a microadenoma and hyperprolactinemia, one with clinical signs of acromegaly. Three of the four patients had abnormal skull x-rays and reduced estrogen production. Two patients had significantly low gonadotropin values. Baseline hormonal testing revealed an elevation of growth hormone in the patient with acromegaly. Other baseline testing was normal. Two of the four patients failed to have an adequate response by LH (one borderline, however) while two had a positive response of FSH to LH-Releasing Hormone. One of the four patients had a negative growth hormone test. All had surgically proven lesions.

Two patients had craniopharyngiomas. Both had positive skull x-rays and decreased estrogen and gonadotropins. One patient had reduced baseline 17-hydroxycorticoids. One patient had a modest response to LH-Releasing Hormone while the other had no response. Neither patient responded to Insulin-HGH testing. Metopirone® testing was not done in one patient, but ACTH testing was normal.

Two patients had the "empty sella" syndrome. Again, skull x-rays were abnormal in both patients and estrogen and gonadotropins were low. Other baseline hormonal testing was normal. Both patients

responded to Insulin-HGH and Metopirone*, but one patient responded poorly to LH-Releasing Hormone. Both patients had this diagnosis confirmed by pneumoencephalography.

Two patients had Sheehan's syndrome with postpartum pituitary necrosis. One patient was clinically panhypopituitary, finding confirmed by low test results of estrogen, gonadotropins, thyroid, and adrenal function. Neither patient responded positively with both LH and FSH to LH-Releasing Hormone or Insulin-HGH. Metopirone* testing was not performed when low serum cortisols were detected. Adrenal response to ACTH was normal.

Four patients had clinical signs of androgen excess with significant hirsutism. Clinical estrogenization was good in all four, but, while baseline FSH was normal, the baseline LH was mildly elevated in all. Laboratory evidence of excess androgen was present in all four patients and was reflected by elevated 17-ketosteroids. Serum testosterone was elevated in two patients with Stein-Leventhal syndrome, and pregnanetriols were elevated in the other two patients who were felt to have adult-onset adrenogenital syndrome. In all four patients there was a normal response of FSH to LH-Releasing Hormone, but an impaired LH response. Other testing was normal.

There were two other patients with organic causes of secondary amenorrhea, one with hypothyroidism and one with premature ovarian failure. Test results are as listed.

Secondary Amenorrhea-Functional (Table 3). Thirty patients had secondary amenorrhea which was felt to be of functional etiology. Patients are divided into diagnoses of anorexia nervosa (4 patients) and "hypothalamic" causes (26 patients). This latter large group is subdivided into patients who had rapid weight loss or gain, stable weight, or had developed amenorrhea after utilizing oral contraceptives. Skull x-rays and physical examinations were negative except for that of weight change, and for four patients who had galactorrhea.

All patients with anorexia nervosa and hypoestrogenism had decreased gonadotropins. Thyroid function was reduced slightly in two

TABLE 2
Secondary Amenorrhea-Organic
(16 Patients)

Diagnosis (No.)	Pituitary Tumor (4)	Cranio-pharyngioma (2)	"Empty" Sella (2)	Sheehan's Syndrome (2)	Androgen Excess (4)
P. Exam	Acromegaly (1) Galactorrhea (1)	V. Fields (1)	–	Hypopit. (1)	Hirsutism (4)
Skull x-ray	+(3)	+	+	–	–
Estrogen	↓ (3)	↓	↓	↓	–
FSH-LH	↑(2)	↓	Normal	↓	FSH Normal LH↑ (4)
HGH, Prolactin, 17OH, 17KS, Thyroid	HGH↑ (1) Prolactin↑ (1)	17OH↓(1)	Normal	17OH↓(1) Thyroid↓ (1)	↑ 17KS (4) ↑ Testos. (2) ↑ PTriol (2)
LRH Test	FSH +2 LH +2	–(1)	sl.↓ (1)	–	FSH+ LH–
Insulin-HGH	–(1)	–	+	–(1)	+
Metopirone*	+	–	+	–	+

Others:
Hypothyroid (1)—Galactorrhea; decreased estrogen, FSH, LH, thyroid studies. Other testing normal.
Premature ●varian Failure (1)—▶ecreased estrogen; elevated FSH and LH. Other testing normal.
+ positive response, or normal test result.
– negative response, or reduced test result.
(See text for details.)

TABLE 3
Secondary Amenorrhea-Functional
(30 Patients)

Diagnosis (No.)	Anorexia Nervosa (4)	"HYPOTHALAMIC CAUSES" (26)				
		Rapid wgt. Loss (4)	Rapid wgt. Gain (3)	Stable wgt. (15)	"Post Pill" (4)	Group Total (26)
Skull x-ray P. Exam	–	–	–	Galactorrhea (3)	Galactorrhea (1)	(4)
Estrogen	↓	↓ (1)	Normal	(4)	(2)	↓ (7)
FSH-LH	↓	↓ (3)	↓ (2)	sl.↓ (2)	↓ (2)	sl.↓ (2) ↓ (7)
HGH, Prolactin, 17OH, 17KS, thyroid	Thyroid sl. ↓ (2)	Normal	Normal	Thyroid sl. ↓ (3)	Prolactin ↑ (1)	Thyroid↓ (3) Prolactin↑(1)
LRH Test	−(3)	−(3)	−(1)	+ +(5) sl.↓ (6)	−(1) sl.↓ (1)	+ +(5) sl.↓ (7) − (5)
Insulin-HGH	+	−(1)	+	+	+	−(1)
Metopirone*	+	+	+	+	+	+

\+ positive response, or normal test result.
− negative response, or reduced test result.

patients. Three of the four patients failed to respond to LH-Releasing Hormone, but all patients had normal responses to insulin by growth hormone and to Metopirone®.

The four patients with rapid weight loss, but not anorexia nervosa, showed better estrogenization, but low gonadotropins also. Similar poor responsiveness to LH-Releasing Hormone was present.

A greater percentage of patients who had rapid weight gain had normal estrogenization, baseline gonadotropins, and normal LH-Releasing Hormone response.

Patients with stable weight who were felt to have hypothalamic amenorrhea were basically normal in estrogenization and baseline gonadotropins. All patients had at least some response to LH-Releasing Hormone, and five had excessive responses. Patients who developed amenorrhea after using oral contraceptives were similar.

The 26 patients with hypothalamic amenorrhea, as a group, were better estrogenized, had more normal gonadotropins, and responded more normally or excessively to LH-Releasing Hormone than did the patients with anorexia nervosa or patients with organic causes of secondary amenorrhea.

Oligomenorrhea. Four patients had oligomenorrhea, two with evidence of ovarian androgen excess. Baseline estrogen, gonadotropins, and other hormone testing were normal except for one patient who was hypothyroid and two hirsute patients in whom there were elevated 17-ketosteroids and serum testosterone. All four patients had positive responses to LH-Releasing Hormone, although in two of these patients the response of LH was borderline. All patients had normal responses to Insulin-HGH and Metopirone®.

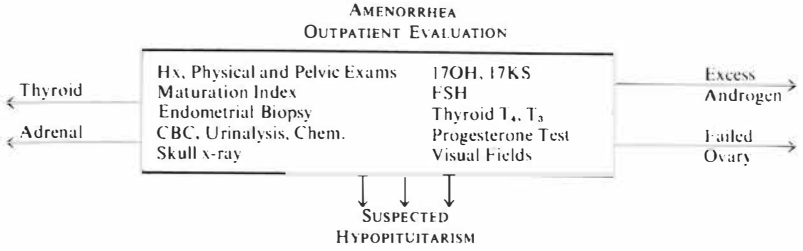
Summary of Studies. In an attempt to summarize these diagnostic studies, one can draw the following conclusions from this group of 58 amenorrheic women:

Skull x-rays are very useful, if positive.

Physical examination is useful when obvious signs of endocrinopathy are present, including acromegaly, hypopituitarism, galactorrhea, or signs of androgen excess. Negative findings do not exclude significant organic pathology, however. Findings suggesting deficiency of a "target gland" (for example, adrenal, thyroid) may be reflections of pituitary-hypothalamic dysfunction rather than peripheral gland abnormality.

Patients with organic causes of amenorrhea are more likely to have clinical hypoestrogenism, and it will tend to be more severe than in patients with "functional" or nonorganic causes. The exception is anorexia nervosa, certainly a severe functional disorder.

FIGURE 1



Baseline serum FSH is of use in identifying gonadal failure, or dysgenesis, when FSH is very high. In problems of androgen excess and functional causes of primary amenorrhea, LH seems likely to be slightly elevated with FSH normal. Gonadotropins are low in patients both with central organic causes and with the more severe functional causes of this problem.

Baseline measurements of growth hormone, prolactin, 17-hydroxycorticoids and 17-ketosteroids, and thyroid hormone all are of great use if abnormal, but usually will require further evaluation.

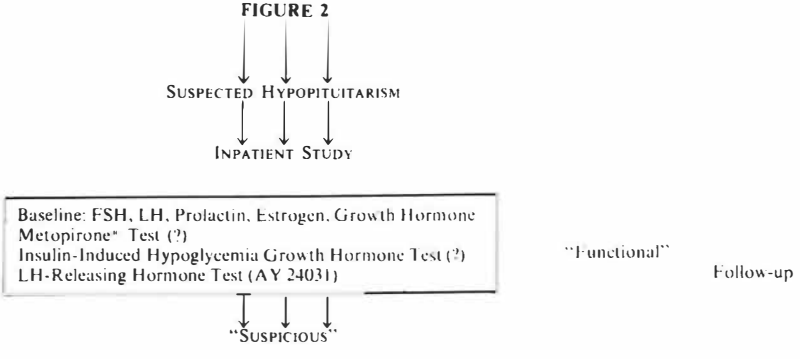
Testing with LH-Releasing Hormone does provide useful information. Patients with organic causes of amenorrhea, other than gonadal failure or androgen excess, were more likely to respond poorly to LH-Releasing Hormone; however, a significant proportion of these patients showed some response with regard to LH, or FSH, or both gonadotropins. Patients with functional disorders more likely had normal or excessive response to LH-Releasing Hormone while those classified as having more severe functional disorders responded very poorly. Growth hormone testing with insulin and Metopirone® testing were of relatively little diagnostic aid unless a major organic etiology was present; an etiology likely demonstrable on skull x-rays, clinical examination, or in patients with more severe abnormalities in baseline hormonal testing.

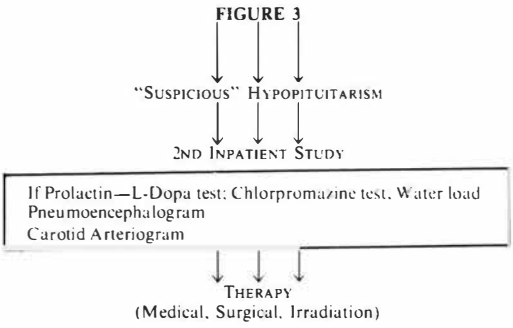
We would again emphasize that these are only *trends* in the results of diagnostic studies in patients who present with amenorrhea. Larger group studies are needed to evaluate the full statistical significance of these data. We would also again emphasize the need for a thoughtful, individualized, sequential evaluation of each patient who presents.

Comment. To reach the goal of individualization in the evaluation of the amenorrheic patient we suggest several possibilities:

Figure 1 illustrates what we consider an adequate screening study for the amenorrheic patient which usually can be done in the outpatient setting. Based on these results, and the clinical findings present, one can categorize problems under thyroid, adrenal, ovarian androgen, or gonadal failure for further studies which can usually be done in the out-

FIGURE 2





patient setting. Some patients will have suspected hypopituitarism and require hospitalization for further study.

Patients with the problem of suspected hypopituitarism should undergo further testing (Fig. 2) as evidenced by the preliminary studies, which should at least include baseline hormonal testing and testing with LH-Releasing Hormone. Growth hormone testing with insulin and/or Metopirone® testing may be indicated, but this must be individualized. Patients who are felt to have "functional" disorders causing amenorrhea are begun on appropriate therapy or follow-up, while patients who are strongly suspected of hypopituitarism usually are studied further.

Further studies (Fig. 3) include tests such as prolactin kinetics, pneumoencephalogram, and possibly arteriogram. If pituitary tumor, craniopharygioma, or other etiology of hypopituitarism is found, then appropriate medical, surgical, or irradiational therapy is initiated.

In this fashion we have tried to present to you the summation of data in 58 patients who presented with amenorrhea, and the endocrinologic testing results that have led to the establishment of a diagnosis. Again, it should be stressed that a systematic, individualized work-up is mandatory for the adequate endocrinologic work-up of the amenorrheic patient.

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Amenorrhea Due to Defects in Steroid Biosynthesis*

H. OLIVER WILLIAMSON, M.D. AND RAJESH S. MATHUR, PH.D.

Department of Obstetrics and Gynecology, Medical University of South Carolina, Charleston, South Carolina

Amenorrhea as the first manifestation of a steroid biosynthetic defect is rather unusual. The common forms of congenital adrenal hyperplasia are classic examples of steroid biosynthetic defects. Yet in genotypic females, this disorder is usually evident from birth because of virilization. Effective treatment usually ensues and amenorrhea is only a problem when control is inadequate. However, there are individuals whose disorder will be manifest for the first time in the postnatal or adult period. In addition, multiple other steroid defects have now been clearly delineated. Many of these individuals will have amenorrhea, virilization, or sexual ambiguities as part of the clinical picture. This paper will describe some of the more clearly delineated steroidal biosynthetic defects. Also, the clinical management of patients with postnatal onset of 21-hydroxylase deficiency form of congenital adrenal hyperplasia will be discussed.

Steroidogenesis. One can better appreciate the biochemical defects and clinical manifestations of these various steroid defects by having a rudimentary knowledge of the basic steroid pathways involved. To pinpoint the individual defects, it is helpful to recall the numbering sequence of the carbon atoms of the steroid molecule as shown in Figure 1. For the purposes of this discussion, one can consider cholesterol as the basic substance from which steroids are derived. It is at the point of its conversion to pregnenolone that tropic hormones have their effect; that is, ACTH for the adrenal cortex, and the gonadotropins for the gonads (Fig. 2). When circulating levels of glucocorticoids or sex steroids reach sufficient levels for physiologic functions of the individual, the classic negative feedback mechanisms become operative so that further releasing hormones from the hypothalamus are held in abeyance, and the specific tropic hormones from the pituitary are not released until there is further need for additional hormones.

In the biosynthetic defects discussed here, the steroid end products necessary for physiological function are not formed in optimum amounts. This triggers release of releasing factors from the hypothalamus which in turn causes secretion of the tropic hormones from the pituitary. Next, stimulation of the target glands (adrenal and/or gonads) leads to excessive intermediate products being elaborated up to the point of the defect. Clinical manifestations of these disorders are due to a deficiency of a normal end product, an excess of intermediate substances with the possible peripheral conversion to other hormones, or usually both. In defects involving steps early in the biosynthetic pathways, the adrenals and gonads are involved. Abnormalities occurring later in the order of flow usually involve only one gland or the other. Important sex steroid precursors and weak androgens may be formed by the adrenal and converted to more potent androgens and even estrogens in certain of these disorders. Such conversions apparently occur in the liver and skin and possibly other tissues. However, the gonads do not form glucocorticoids.

Specific Defects. Brief descriptions of biosynthetic defects will be outlined starting at the more

* Presented by Dr. Williamson at the 46th Annual McGuire Lecture Series, December 5, 1974, at the Medical College of Virginia, Richmond.

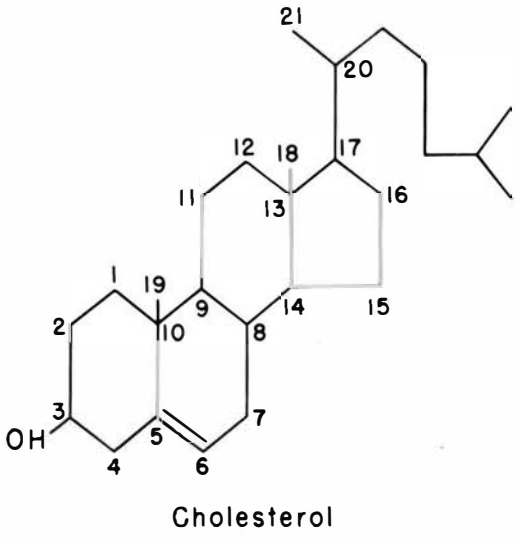

Fig. 1—Numbering sequence for the first 21 carbon atoms in steroid nomenclature. Useful in locating biosynthetic steroid defects described in this paper.

primitive, or early, stages of steroid biosynthesis and proceeding to later-stage defects. Accordingly, the order of presentation bears no relationship to relative frequency or importance of these disorders.

C-20 block with lipoid adrenal hyperplasia (Desmolase deficiency CAH) (Fig. 3). Being unable to convert cholesterol to pregnenolone, affected individuals lack life-sustaining steroids; hence the disorder is fatal. The condition is of interest to the gynecologist in that it supports Jost's work regarding virilization of the genital tracts. Being a primitive (early) defect, it involves steroidogenesis in the gonads as well as in the adrenals. The fetal testes are unable to form adequate androgens to virilize the genitalia fully, leading to genital ambiguity in genetic males. This is in contradistinction to the findings in the more common 21- and also 11-hydroxylase forms of congenital adrenal hyperplasia where genetic females are often born with ambiguous genitals. Cholesterol accumulates in the adrenal of affected individuals; hence the designation "lipoid." Theoretically, the treatment would be the administration of glucocorticoids and mineralocorticoids with the addition of appropriate sex steroids at the time of pubescence. Prader, Gurtner, and Siebenmann (1, 2) reported two patients with this disorder and collected five additional cases. All seven died before the eighth month of life with adrenal insufficiency even though treatment with gluco- and mineralocorticoids had been employed. Although other steroid abnormalities may be present, it is probable that the main defect is in the transformation of cholesterol to pregnenolone (3). Early fatalities preclude this form of CAH in the differential diagnosis of amenorrhea, though ultimately a mild form of the defect with survival might be anticipated.

Three β-hydroxysteroid dehydrogenase deficiency (Fig. 4). Being unable to convert pregnenolone to progesterone, these individuals present with many of the features of the previously described desmolase deficiency. Salt loss has been a prominent feature of the adrenal insufficiency with the result that fatalities are usual. Inadequate testosterone leads to ambiguous genitals in genetic males whereas mild virilization of affected females has been attributed to testosterone being formed from increased amounts of dehydroepiandrosterone (DHA) and other precursors. Since it is a primitive defect, gonadal steroidogenesis is also affected. In Bongiovanni's series (4), three females out of a total of six individuals with this form of CAH were surviving. He postulated a partial defect as did Kenny and his coworkers (5). The latter authors also showed increasing 3β-hydroxysteroid dehydrogenase activity with increasing age. Steroid excretion patterns in these patients would suggest the development of alternate pathways which allow for survival of some infants. The presence of pregnenetetrol (with a hydroxyl group at C 21) suggests the ability of 17-hydroxylase and 21-hydroxylase to act on this "primitive" molecule (6). This compound is not excreted in increased amounts in the usual 21-hydroxylase deficiency (7). Since this enzyme also plays an important part in the gonadal biosynthesis of sex hormones (6), its absence would necessitate substitutional sex-hormone therapy at pubescence. Obviously sterility can be anticipated.

Seventeen α-hydroxylase defect (Biglieri syndrome) (8) (Fig. 5). This being a primitive block, the gonads and adrenals are involved. Absence of adequate sex steroids leads to hypogonadism and elevated gonadotropins. The elevated levels of desoxycorticosterone (DOC) and corticosterone lead to hypokalemic alkalosis and hypertension, thus turning off the renin-angiotensin mechanism with resultant low or absent aldosterone. This defect is clinically ex-

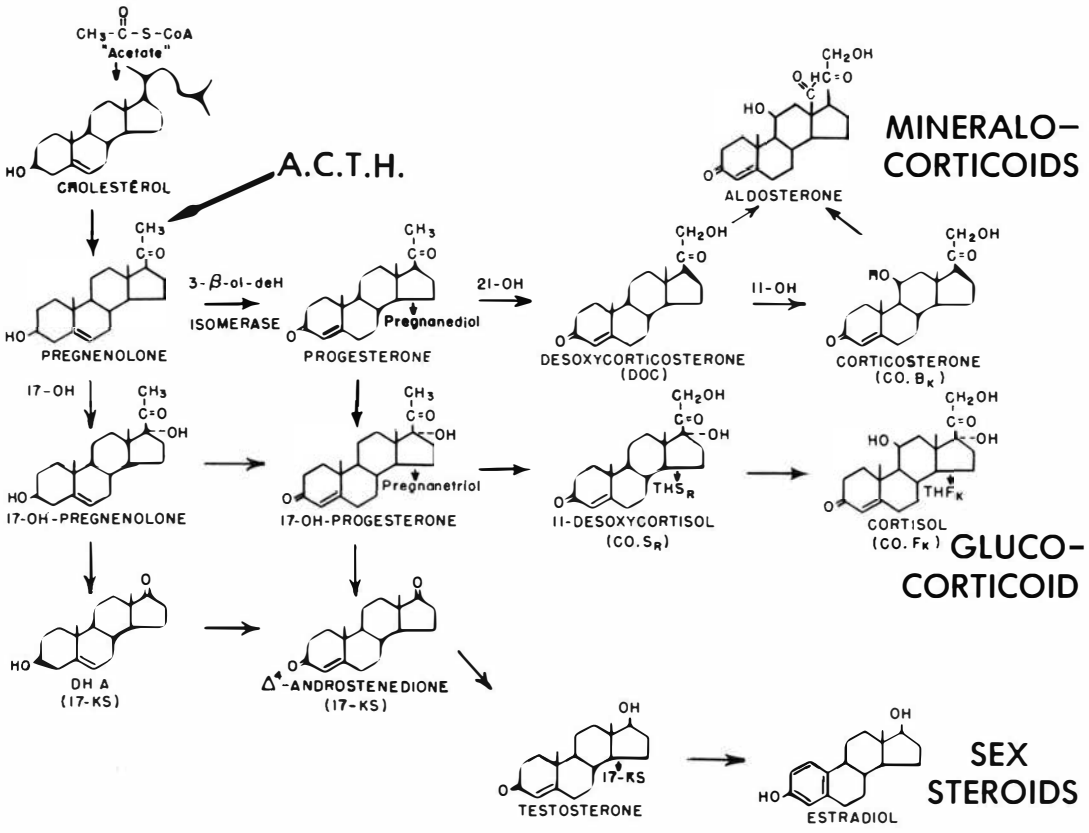

Fig. 2—Abbreviated steroid flow sheet of major steroids produced in the human. Mineralocorticoids are regulated by a mechanism involving osmolar and pressor receptors and in turn the renin-angiotensin mechanism and only to a minor degree by ACTH. The glucocorticoid (cortisol) plasma levels are modulated by negative feedback influence of the 11-hydroxyl group on the hypothalamus and in turn its releasing factor for ACTH. The major sex steroids, testosterone and the estrogens, typified by estradiol, are produced from adrenal DHA and androstenedione in tissues peripheral to the adrenal such as the liver and the skin. Some degradation products of major steroids are pointed out by small arrows beneath the individual steroids.

pressed in the genetic female by hypertension and the absence of puberty. In addition to the elevated gonadotropins, blood progesterone is high. In the genetic male, ambiguous genitalia and absence of puberty result from the inability to make either androgens or estrogens; hence it is a cause of male pseudohermaphroditism (9). This syndrome in genetic females is similar to the feminizing testicular syndrome in the absence of secondary sex hair, but differs in that breast development is absent and hypertension is present. The treatment in females is adequate substitutional therapy with glucocorticoids. Preference is given to one without significant mineralocorticoid activity; for example, prednisone. Addition of sex steroids at pubescence is indicated, but infertility can be expected. It would appear that these patients could be monitored for effectiveness of therapy by the measurement of plasma progesterone.

Simple virilizing congenital adrenal hyperplasia (mild 21-hydroxylase defect) (Fig. 6). Being unable to form optimal amounts of cortisol and corticosterone, these individuals exhibit augmented ACTH production which leads to shunting towards the androgen pathway and ultimate virilization. Aldosterone and cortisol (hydrocortisone) are formed in suboptimal amounts so that overt adrenal insufficiency may not be necessarily manifest (10, 11). The majority of female patients will have exhibited considerable evi-

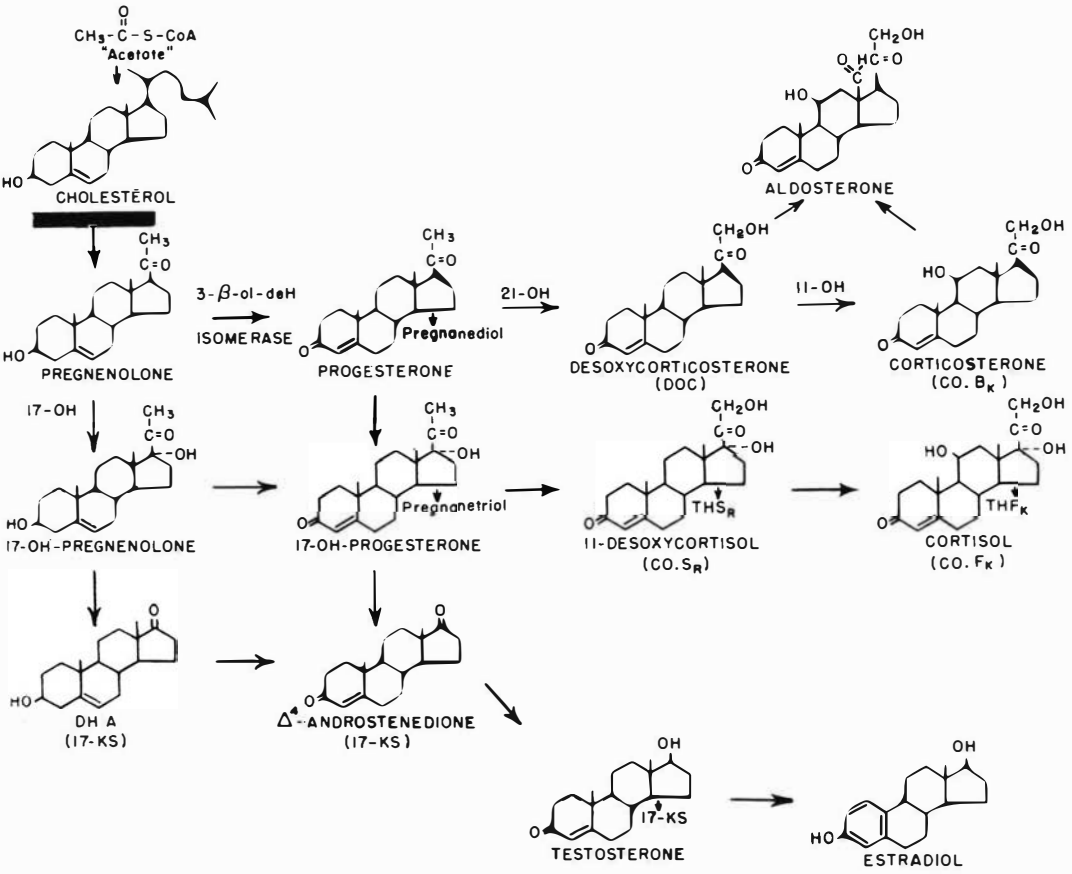

Fig. 3—Desmolase defect (also called lipoid adrenal hyperplasia due to accumulation of cholesterol in adrenals). Usually fatal due to deficiency of both mineralocorticoids and glucocorticoids. Leads to sexual ambiguity in males due to deficient testosterone to masculinize in utero.

dence of virilization and usually sexual ambiguity at birth, leading to prompt diagnosis and treatment. In the affected male, however, the external genitalia are normal and the diagnosis of CAH is therefore less obvious. This doubtless accounts for the predominance of the disorder in females; that is, males may die of undiagnosed hypoadrenalism.

Diagnosis and treatment depend largely on suppressibility of the hyperactive hypothalamic-pituitary-adrenal axis by exogenous administration of 11-hydroxylated glucocorticoids. Androgens are elevated in plasma and urine. Estrogen excretion may be elevated in these individuals (12, 13). Such estrogenic activity is not clinically manifest. Presumably, the excessive androgens effectively override the estrogenic activity. Most investigators have held that urinary gonadotropins are suppressed by the excessive androgens (13, 14). However, Stevens and Goldzieher (15) found detectable and often adult levels of gonadotropins in 4 of 5 children with CAH and variable levels in adults. Steroid suppressive therapy led to a fall of FSH in 3 of 6 patients whereas LH was unchanged in 5 and rose in 2, suggesting that compensatory pituitary hyperactivity in CAH is not limited to the pituitary adrenal mechanism but has repercussions in gonadotropin regulation as well. In

any event, once adequate suppressive therapy is instituted, postpubertal females rapidly feminize and become ovulatory.

Diagnosis can be suspected on the basis of baseline urinary 17-ketosteroids (17-KS). Normal adult females ordinarily have values between 2 and 12 mg/24 hours. Patients with obesity, stress situations, essential and familial hirsutism or Stein-Leventhal syndrome may have levels to 25 or even 30 mg/24 hours whereas patients with CAH usually will have baseline values on the order of 50 mg/24 hours. Patients with adrenal adenomas ordinarily will have values of approximately 100 mg, and patients with virilizing adrenal carcinomas will have values of 200 mg or up. The degradation metabolite of 17 hydroxyprogesterone (17OH-P), pregnanetriol, was found to be elevated in the urine of these patients and has been used for years to confirm the diagnosis and to monitor therapy. Most laboratories report normal values in adult females to be 4 mg or less per 24 hours. Patients with CAH have values from modestly above 4 mg up to manyfold this level. The suppressibility of this steroid as well as 17-KS by 2 mg of dexamethasone every 6 hours for two days proves the ACTH dependence of the disorder and differentiates it from the autonomous virilizing adenomas and carcinomas (16). However, it appears that pregnanetriol is not a primary intermediate in the formation of an-

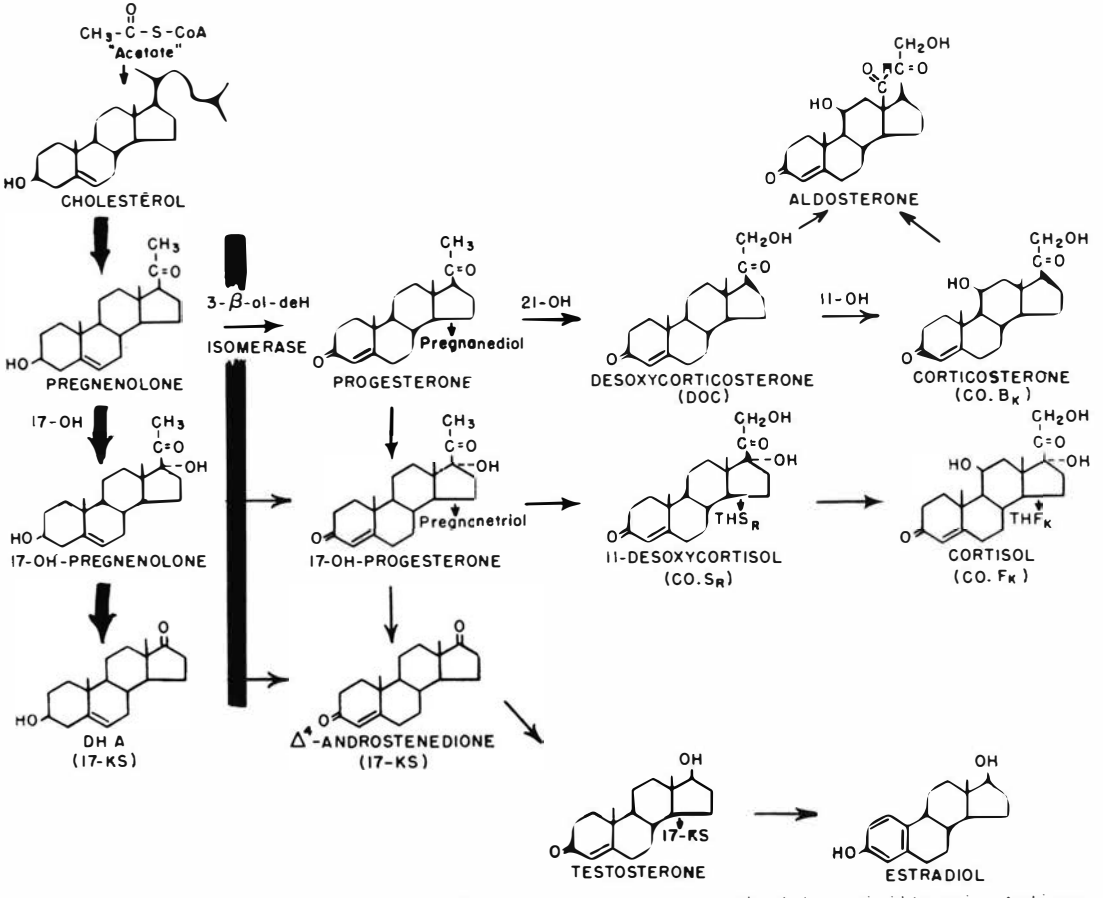

Fig. 4—Defect of 3β ol-dehydrogenase-isomerase. Fatal due to decreased mineralocorticoid and glucocorticoid formation. Ambiguous genitals in males due to deficient androgen production to fully masculinize in utero. Partial virilization of females due to peripheral conversion of DHA to androgens.

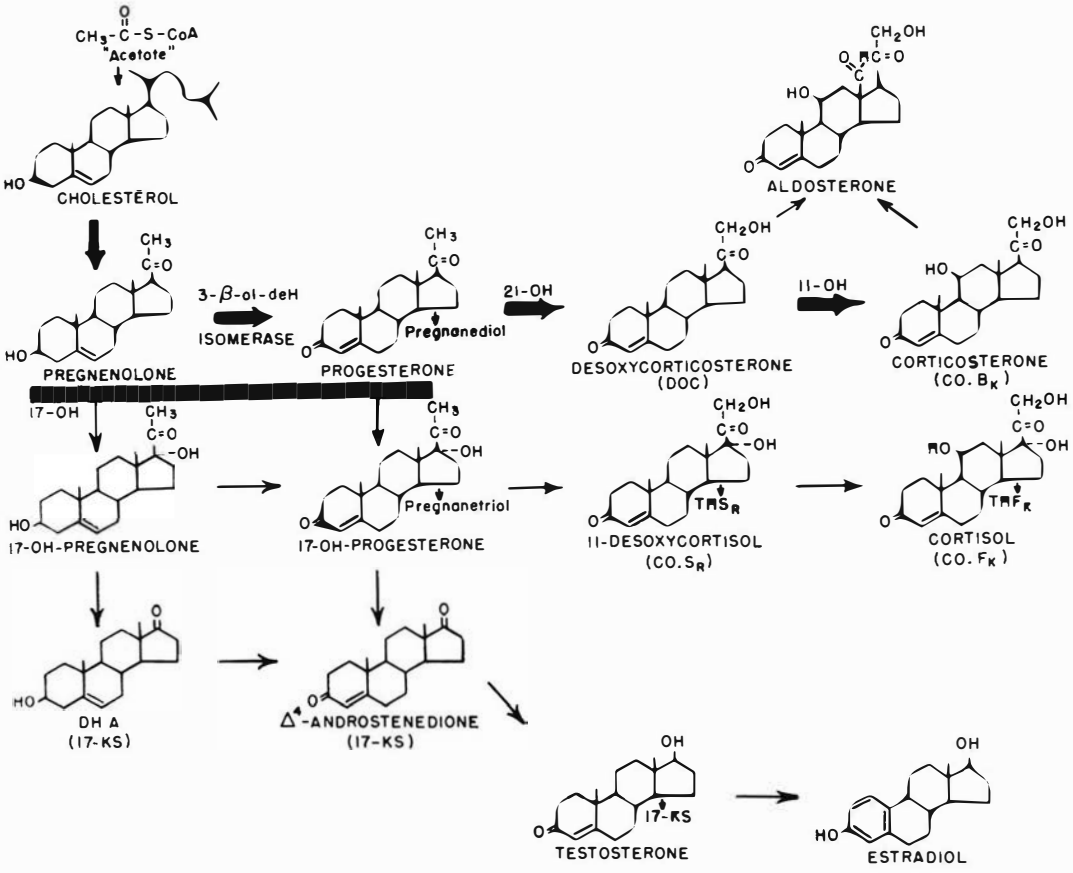

Fig. 5—Seventeen α-hydroxylase defect (Biglieri syndrome). Accumulation of mineralocorticoids leads to hypertension and deficiency of sex steroids to absence of secondary sex characteristics in females and failure to develop external genitalia in males.

drogens (17) suggesting that the major pathway is through DHA and androstendione. Although 17OH-P has been known to be elevated in this disorder for years (18), its measurement as a practical matter has been of more recent vintage (19, 20). The bother and inaccuracy of collection of 24-hour urine specimens for steroid assays has led to the measurement of plasma 17OH-P, progesterone, and testosterone in diagnosing and monitoring these patients. Lippe and co-workers point out multiple factors that may affect serum steroid determinations (21); hence they suggest that where virilization is a prominent feature in amenorrheic women, long-term adrenal suppression tests with measurement of several plasma steroids (for example, 17OH-P and testosterone) be utilized. Normal adult patients ordinarily have plasma 17OH-P levels of up to 200–400 ng% whereas patients with CAH and blocks of C-21 or C-11 hydroxylation will have levels severalfold that amount when untreated or if out of control (for example, 1–4 μg%) (19).

A subvariant of the mild 21-hydroxylase deficiency is that of the postnatal onset of the disorder. Sporadic cases have been reported (22, 23, 24) and described. It would appear that these individuals have a milder form of the disorder which becomes manifest only upon their being stressed.

Other subvariants of the 21-hydroxylation deficiency include periodic fever in association with

elevated plasma etiocholanolone (25) and "late" sodium loss (26). Hypoglycemia probably is not a separate subvariant but a manifestation of hypoadrenalism.

Severe 21-hydroxylase defect (salt-losing congenital adrenal hyperplasia) (Fig. 7). This variant of the 21-hydroxylase defect is more complete so that a deficiency of mineralocorticoids including aldosterone exists. Shunting to the androgenic pathway is also present leading to virilization. The defect, being of more profound degree, leads to even higher ACTH levels than in the simple virilization syndrome so that hyperpigmentation may ensue and indeed has been used as a clinical sign in addition to steroid assays in the monitoring of therapy. Diagnosis is the same as with the mild form, but treatment differs. In addition to suppressive therapy with a glucocorticoid, a mineralocorticoid and often salt supplementation are necessary. It has been suggested that different 21-hydroxylation defects may exist in the salt losers as opposed to the nonsalt losers (27).

Eleven-hydroxylase deficiency (hypertensive congenital adrenal hyperplasia) (Fig. 8). In addition to the shunting along the androgenic metabolic pathway as in the 21-hydroxylase defects, the mineralocorticoid, DOC, accumulates, leading to salt retention and hypertension. These patients also frequently pigment

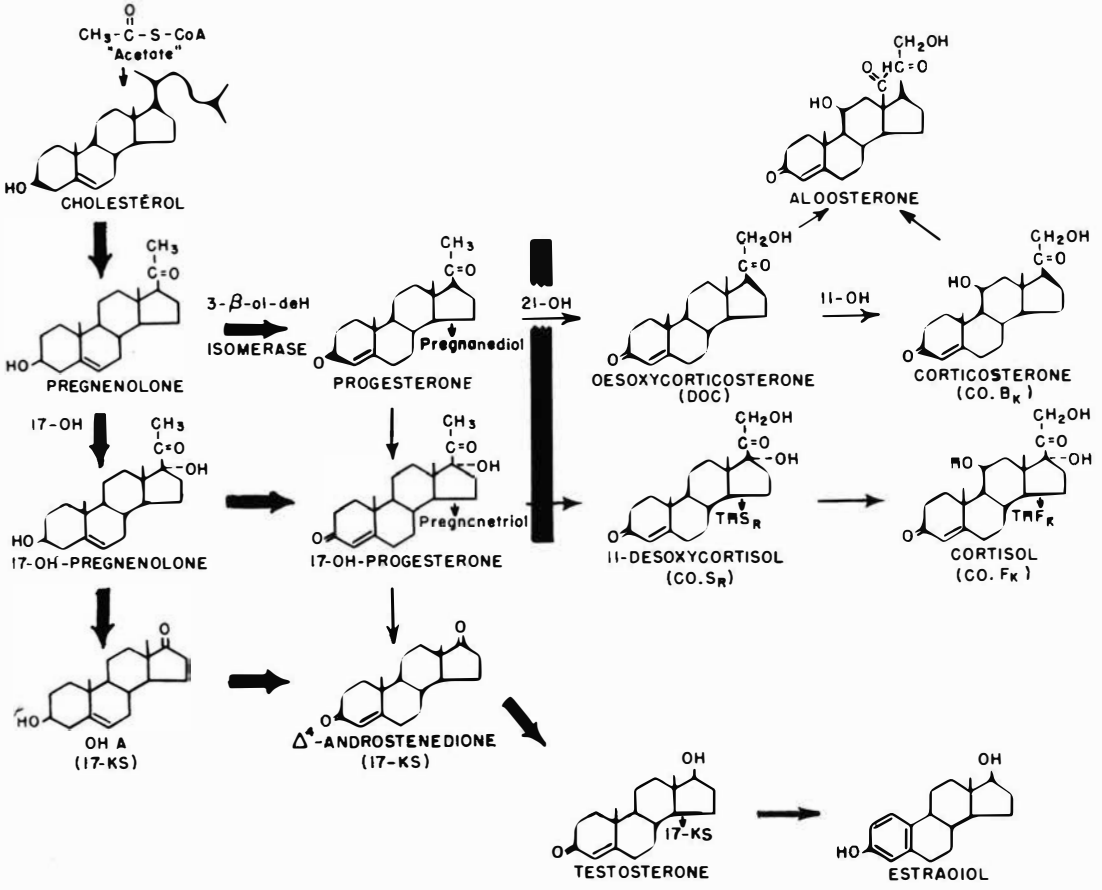

Fig. 6—Mild 21-hydroxylase defect. Glucocorticoids and mineralocorticoids may be formed, but at expense of adrenals becoming hyperplastic with overt production of androgen precursors which are converted to testosterone. This leads to virilization in adults, somatic precocity and pseudohermaphroditism in female infants.

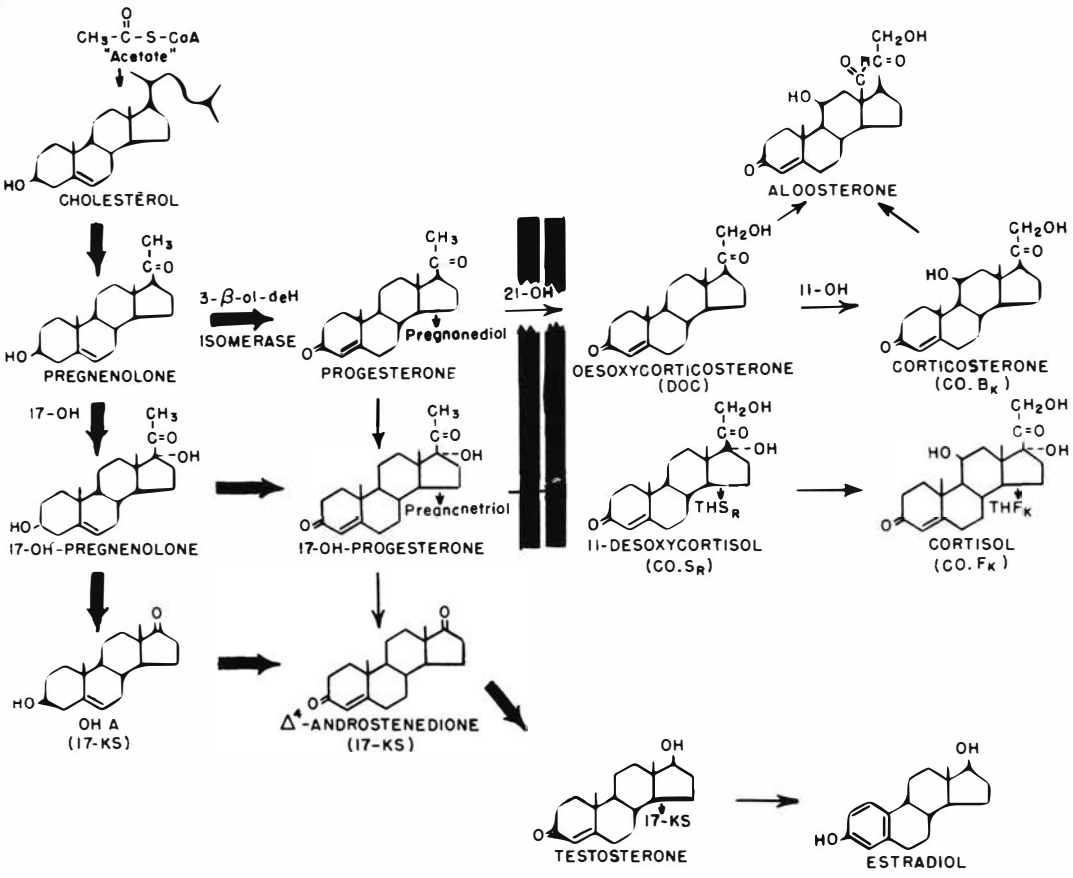

Fig. 7—Severe 21-hydroxylase defect. Virilization findings similar to the mild form but additionally salt loss occurs due to the mineralocorticoid deficiency including aldosterone.

from the excessive ACTH activity. Clinically, these patients present as the 11-hydroxylase patients except for hypertension and salt retention. Diagnosis can be suspected on the basis of hypertension. Biochemical confirmation is by the finding of elevated levels of tetrahydro-S (the degradation product of 11-desoxycortisol) in the urine. More specific radioimmunoassays for DOC and 11-desoxycortisol may simplify diagnosis in the future.

Late onset of this disorder has also been reported (28, 29). Zachmann and co-workers extensively studied an infant girl with an 11-hydroxylase deficiency who was normotensive and had normal levels of DOC though compound S was excessively high. This suggested to them a selected inhibition of the 11β-hydroxylation of 17α-hydroxylated steroids (30).

Eighteen-hydroxylase dehydrogenase defect (Fig. 9). Ulick (31) described this disorder accompanied by low aldosterone resulting in low serum sodium, high potassium, dehydration, hypotension, high renin activity, and elevated levels of hydroxycorticosterone. This disorder should not enter into the differential diagnosis of amenorrhea and the virilizing congenital adrenal hyperplasias.

Seventeen β-hydroxysteroid dehydrogenase defect (deficient testicular 17-ketosteroid reductase activity) (Fig. 10). Goebelsmann and co-workers (32)

described a 46-year-old married phenotypic female with clitoral enlargement, hirsutism, breast development, and a blind vaginal pouch. Chromosomal karyotype was 46 XY. Abdominal testes were removed. Prior to operation, testosterone was at low normal male levels, though considerably above female levels. Urinary 17-KS were 33 mg/24 hours. The finding of androstenedione of 1.02 μg/100 ml (being tenfold above normal male levels) suggested testicular 17β-hydroxysteroid dehydrogenase deficiency. More recently, Givens and associates (33) described two additional patients (sisters) with primary amenorrhea, hirsutism, clitoral enlargement, 46 XY karyotype, but lacking breast development. They, too, found grossly elevated androstenedione levels along with elevated urinary 17-KS and plasma estrone, but subnormal amounts of testosterone and estradiol. In vitro incubation of testicular tissue from their second case confirmed a partial defect in testicular 17-KS reductase activity and documented increased 3β-hydroxysteroid dehydrogenase activity. They felt that failure of breast development was probably due to lower estrogen levels than in previously reported cases. Accordingly, when one finds elevated 17-KS in an amenorrheic individual, further delineation of the defect by steroid biochemical assays seems warranted. Indeed, such investigations may show the Reifenstein syndrome as well as other forms of male

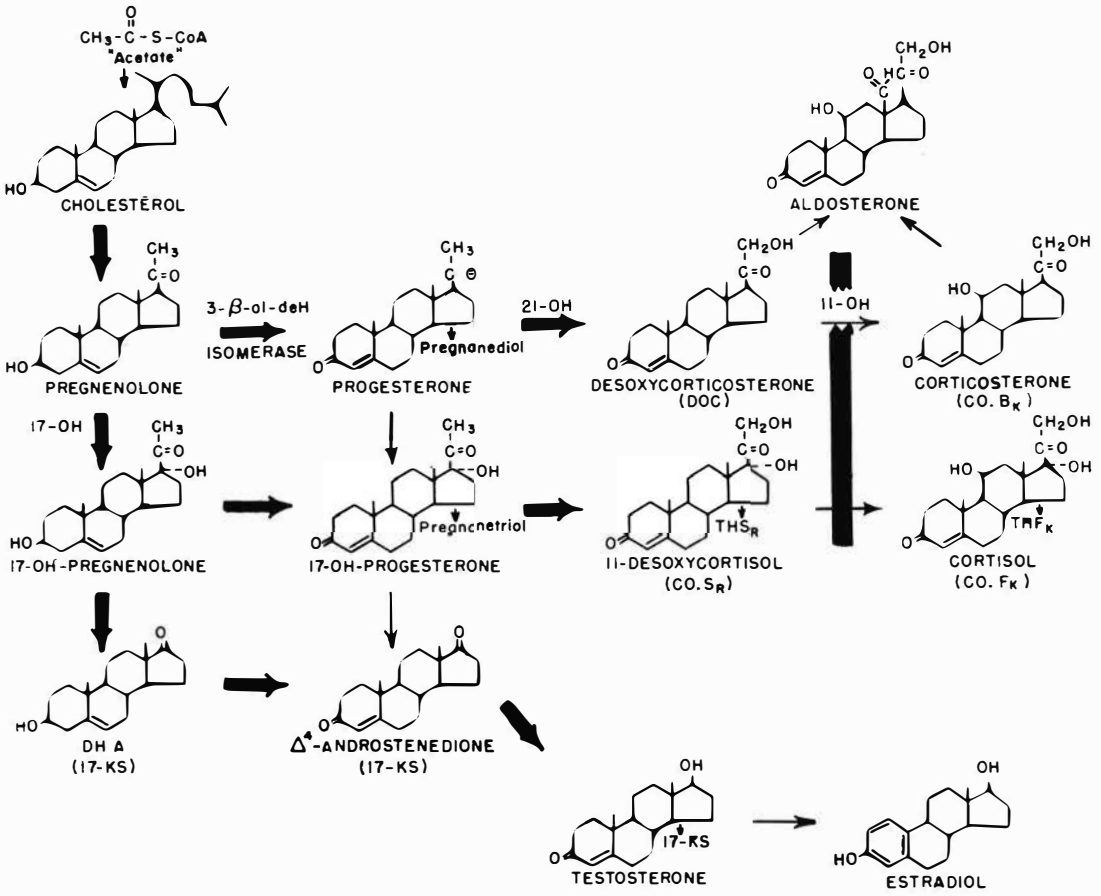

Fig. 8—Eleven-hydroxylase defect. Virilization due to shunting of adrenal precursors to androgenic pathway. Hypertension results from accumulation of mineralocorticoids—principally desoxycorticosterone.

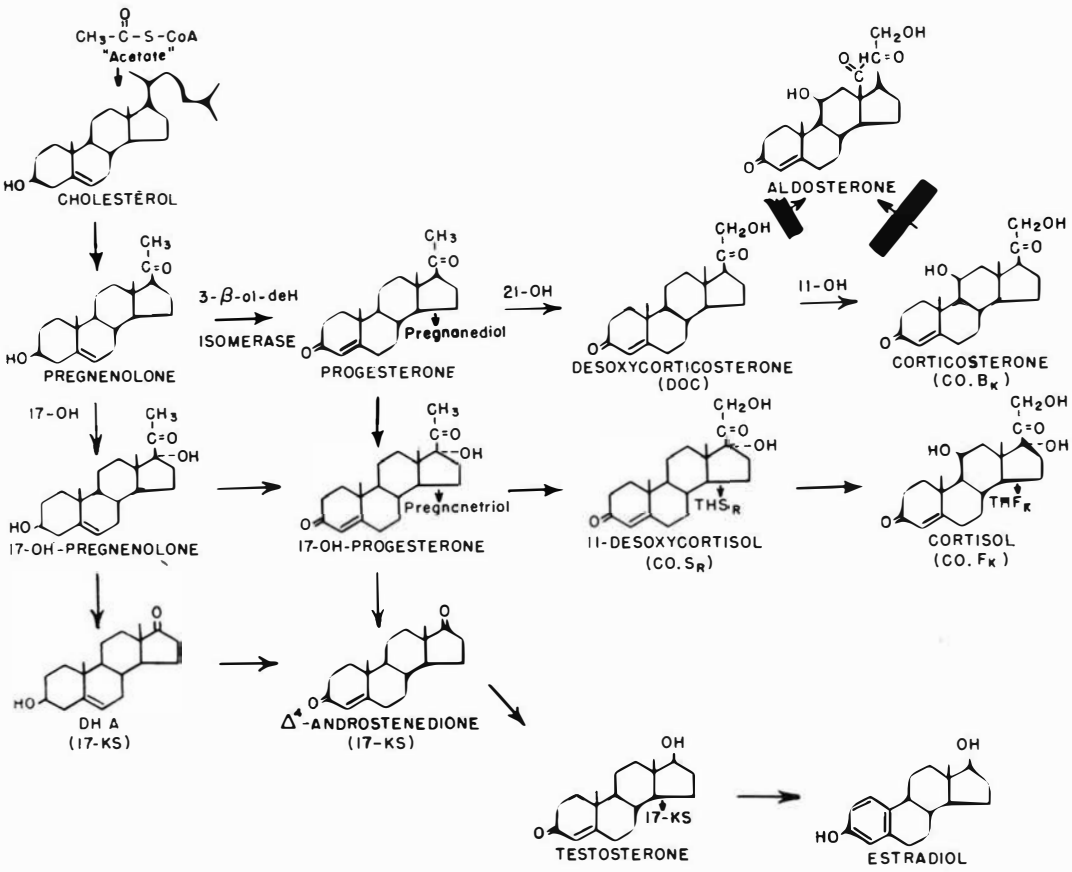

Fig. 9—Defect of 18-hydroxylase dehydrogenase. Aldosterone deficit leads to decreased plasma sodium, high potassium, dehydration, hypotension, and high renin activity. No direct gynecologic endocrinopathy association.

pseudohermaphroditism to be due to this disorder of steroid biosynthesis.

Stein-Leventhal syndrome (Fig. 11). Early workers dealing with in vitro studies showed an accumulation of DHA and testosterone in incubation studies on ovarian tissue from patients with this syndrome. These studies suggested a partial defect in the aromatizing enzyme to convert testosterone to estradiol as well as an inadequacy of 3β-ol dehydrogenase activity. However, such observations were not interpreted to imply the uniform existence of invariable, all-or-none enzyme defects in the polycystic ovarian tissue (34). Accumulating evidence would suggest, however, that the issue is much more complex. Probably there are patients now classed with this syndrome whose disease primarily resides in the adrenal cortex, others who have primarily an ovarian defect; but the majority have a defect in hypothalamic function. Accordingly, it is felt that there is no such neat demonstration of a consistent biochemical defect as outlined in Figure 11 in spite of early works suggesting such.

Case Presentations. *Post-pubertal simple virilization.* Patient M.S.H., Duke Unit #5-59154 (Fig. 12). A 17-year-old female was seen on referral November 1, 1961, with defeminization. Menarche was at 11 years with regular menses for two years. At age 13, the patient had mumps and measles during a two-

week period. Infrequent and scant menses, averaging one per year followed. Acne and hirsutism steadily progressed after age 11. Loss of scalp hair had progressed for 5 months. Patient was said to be the product of a normal term delivery, though she was adopted. Pertinent laboratory findings are noted in Table I. Two rest days intervened between the ACTH, metapyrone, and dexamethasone tests. Suppressive therapy was started, and the patient had an ovulatory spontaneous menstrual period 6 weeks later proved by endometrial biopsy. She was married, and while on suppressive therapy, delivered spontaneously on January 1, 1967, under pudendal block anesthesia, a 5 lb. 8 oz. normal male infant and on November 21, 1968, a 6 lb. 15 oz. normal female infant by Dr. William A. Peters. Her pelvis was normal by x-ray pelvimetry. During each delivery, the patient was supported by parenteral hydrocortisone, and her oral glucocorticoid was doubled then gradually tapered to maintenance level during the immediate puerperium. In that the patient appeared so normal and was cycling spontaneously, glucocorticoid therapy was discontinued in September 1969. She has continued to have cyclic menses without evidence of virilization. During the past year, her urinary 17-KS were 13.7 mg/24 hrs on two occasions, and her 17-hydroxycorticosteroids (17OH-CS) 2.9 and 4.3 mg/24 hours.

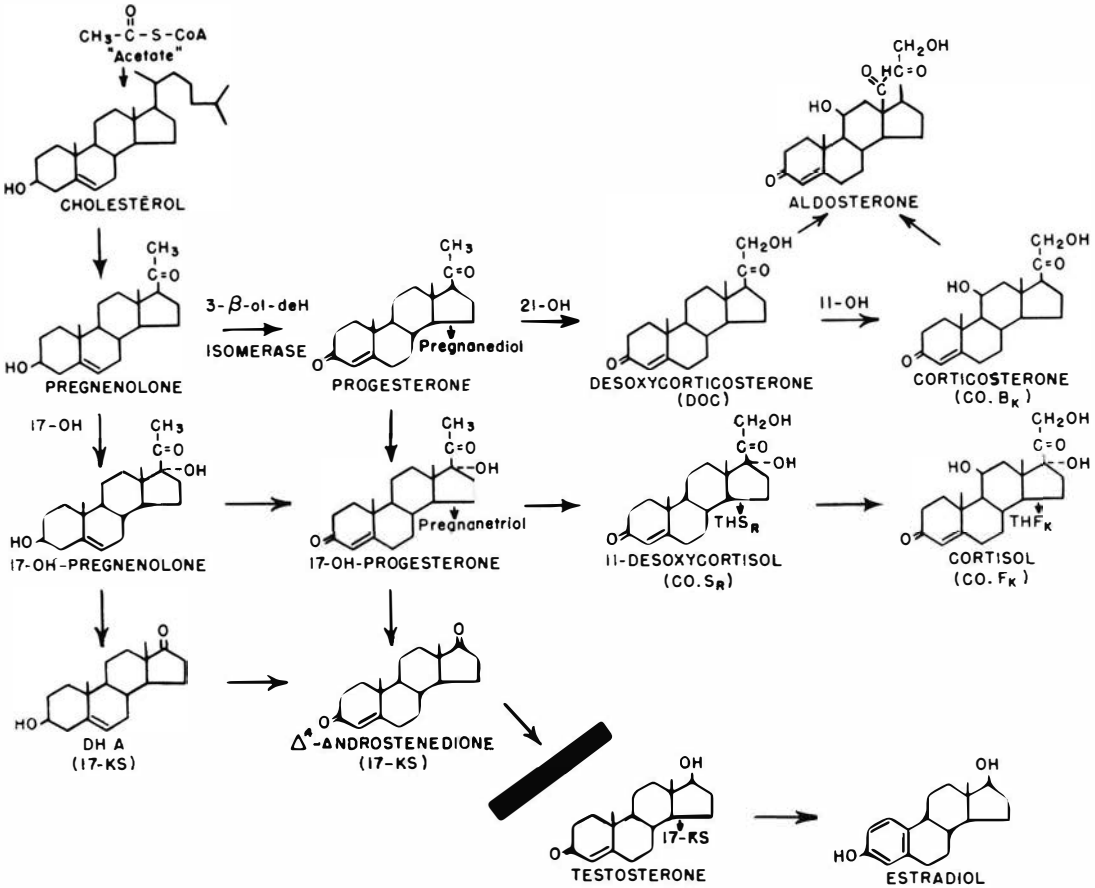

Fig. 10—Defect of 17β-hydroxysteroid dehydrogenase. Extremely rare steroid defect where androstenedione increased some tenfold over normal levels while achieving low normal testosterone. Reported in male pseudohermaphrodites, hence a consideration in differential diagnosis from common forms of CAH.

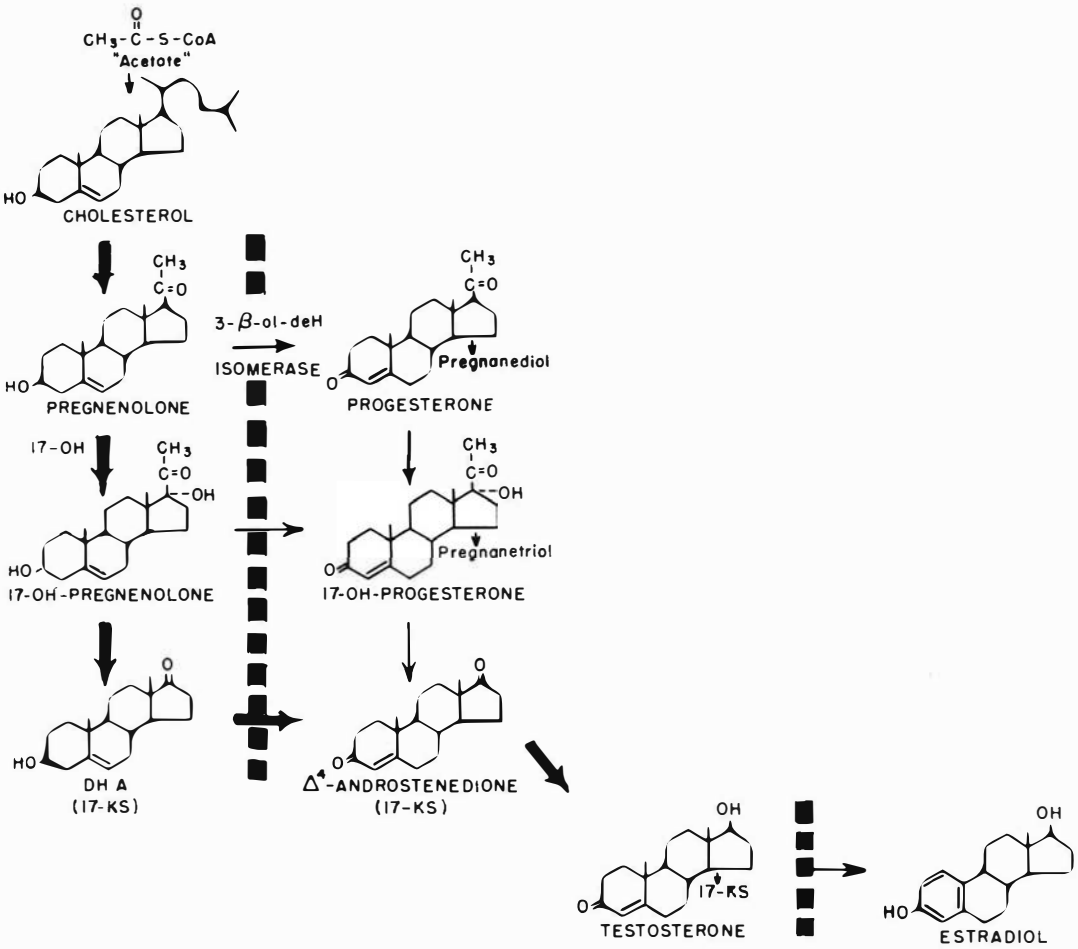

Fig. 11—Aromatization defect leading to excessive accumulation of testosterone and partial 3β-ol dehydrogenase defect causing elevated levels of DHA described inconsistently with Stein-Leventhal syndrome.

Comment. Postnatal virilization of the female is more commonly due to an autonomous tumor or ingestion of hormones than due to the postnatal (acquired) form of congenital adrenal hyperplasia. However, ready suppressibility of this patient's greatly-elevated abnormal steroids bespeaks the nature of her disorder. Since her onset occurred after most, if not full, statural growth had been achieved, she was not stunted, nor was her pelvic capacity compromised. Accordingly, delivery was spontaneous. Her children have been assessed for the possibility of congenital adrenal hyperplasia, and this has been ruled out. The chances of offspring having the disorder are remote, since the prevalence of the gene for the disorder is on the order of 1 in 128 for heterozygotes and 1 in 67,000 for the overt disease (35). However, the frequency will be on the increase in that affected individuals with proper treatment will no longer be sterile (36). This patient is remarkable in that she has remained apparently normal for a protracted period of time off of therapy in spite of a severe abnormality of steroidogenesis when first diagnosed. Her 17-KS are now upper limits of normal and her 17OH-CS are low bespeaking the fact that she

probably is just minimally compensated. However, she has undergone the stress of rearing two small children and moving to Europe without decompensating. Accordingly, our original hypothesis of decompensation due to psychologic stress of adolescence may be questioned (37).

Postnatal simple virilization. Patient K.S.S., Unit # 61682 (Fig. 13). A 13-year-old white female was seen January 18, 1963, because of "virilizing syndrome." She was born prematurely. Development was normal until age 4 when pubic and axillary hair became apparent. Her 17-KS were elevated, and glucocorticoid therapy was given elsewhere for two years, but discontinued by the mother when Cushingoid features developed. These rapidly disappeared, but were followed by progressive hirsutism. One brother had prostatic hypertrophy diagnosed at age 19.

Suppressive therapy was started January 23, 1963, and the patient was hospitalized elsewhere April 3, 1963, with right lower quadrant abdominal pain. Fifteen days later, menarche occurred and was followed by regular menses and rapid budding of breasts. Hirsutism gradually decreased, but her voice remained unchanged. Significant laboratory data are shown in Table I. Iliac crests were fused on the abdominal film. With her last menstrual period in May 1967, and after an adequate trial of labor, patient was delivered by cesarean on February 5, 1968, of a 5 lb. 7 oz. normal female. Opera-

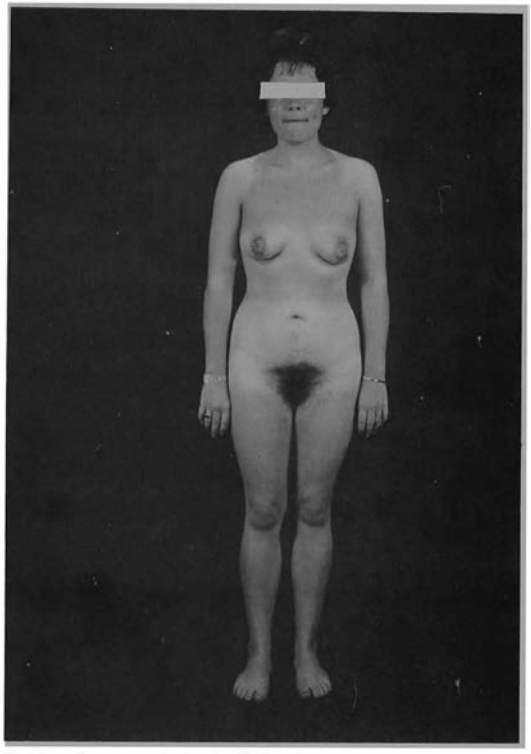

Fig. 12—Patient M.S.H., #F-59154. Normal feminine contour and endocrine measurements existed with comedones and facial hirsutism. B.P. 120/70. Weight 61 kg.

TABLE I

Patient	Age	Therapy	Urinary Steroids 17-KS	17-OH-CS	17-Ketogenic	Pregnanetriol
M.S.H.	17	None	82.8	11.4	15.7	9.7
		ACTH Gel 40 U IM q. 12 hrs. × 3 days	164.7	31.0	156.6	24.9
		Metapyrone 500 mg q. 4 hrs. × 2 days	77.4	41.8	128.0	43.2
		Dexamethasone 0.5 mg. q. 6 hrs. × 2 days	41.8	1.4	9.8	2.9
		Dexamethasone 2 mg. q. 6 hrs. × 2 days	7.8	0	3.6	0.5
K.S.	13	None	40.1			71.3
		Dexamethasone 0.5 mg q. 6 hrs. × 2 days	18.3		107.8	
		Dexamethasone 0.5 mg q. 6 hrs. × 2 days	7.6		31.4	
		Dexamethasone 2 mg. q. 6 hrs. × 2 days	5.7	2.7	11.6	1.4

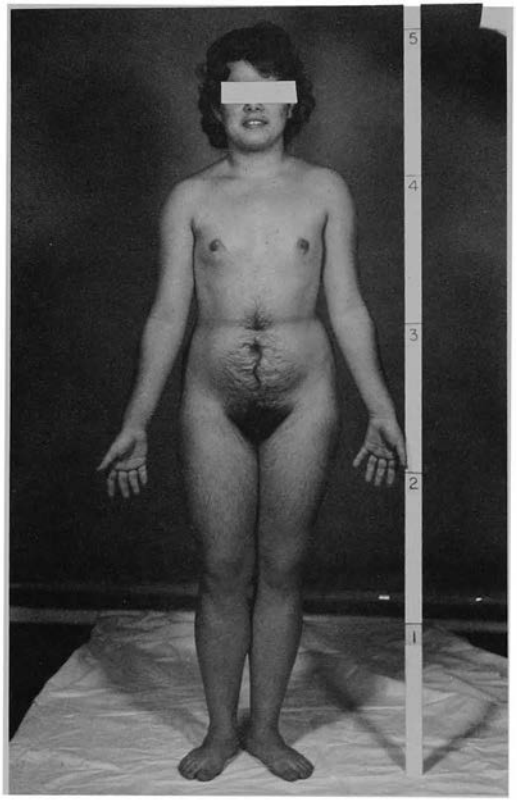

Fig. 13—Patient K.S.S., # 61682. Shows stunted growth, facial hirsutism, and android escutcheon. Chest was shaved prior to photography. Muscle hypertrophy was present and breast development absent. Voice was baritone. B.P. 150/90. Weight 55.5 kg. Height 152 cm. Span 151 cm. Lower segment 76 cm.

tion was necessary due to a moderately contracted pelvis of somewhat android configuration.

The patient has been maintained on prednisone 5 mg at bedtime. She continues to cycle normally. Her plasma 17OH-P of 216 ng%, plasma progesterone 1.4 μg% in luteal phase with plasma estradiol 20.3 ng%, suggest ovulation. However, her plasma testosterone persisted in the range from 80 to 120 ng% bespeaking continuing excessive testosterone production. Accordingly, an additional 2.5 mg of prednisone is being added in the morning.

Comment. Failure to continue glucocorticoid therapy as prescribed by her physician led to premature closure of this patient's epiphyses and ultimate stunting from excessive sex steroids. In turn, this probably necessitated delivery by cesarean because of cephalo-pelvic disproportion. In the past, some patients with adrenal hyperplasia who could not tolerate steroid therapy have been subjected to adrenalectomy. However, such surgical therapy is no longer warranted, for proper monitoring should be achievable so that the disease can be brought under control without significant side effects from the medication. Hayek and associates have suggested the single dose of a long-acting suppressive agent at midnight for therapy of this disorder with good results; hence simplifying therapy (38). Such therapy is appealing and rational. However, one must use a fairly long-acting steroid; therefore, oral hydrocortisone, the naturally occurring hormone that is missing, can not be utilized. Problems persist in such patients as this who have their sleep-wake patterns altered by work habits (she is a telephone operator working swing shifts). This may account for the need for an additional a.m. dose. Reversibility of some signs of virilization occur (the patient has lost much body hair, though some facial shaving is still necessary). Rapid feminization as shown by breast development and ovulatory menses is to be expected once adequate therapy is instituted. Her hospitalization was for suspected appendicitis, but the pain was apparently mittelschmerz, since she had her menarche two weeks later. Clitoromegaly and deep voice have persisted in this patient, since such changes, once they occur, do not reverse. Contraception in this patient, as well as in the first, is by intrauterine device. Estrogen-containing oral contraceptives should be avoided in as much as they confound steroid monitoring of such patients by altering steroid binding proteins. This patient was found to be hypertensive when initially seen, raising the question of a possible 11-hydroxylase block. However, measurement of tetrohydro-S showed no significant amounts of this in the urine. Prolonged hypertension following cessation of desoxycorticosterone therapy in CAH has been reported (39); however, we feel that this is highly unlikely in this patient, since initial therapy had been discontinued for almost a decade before she was found hypertensive.

Patient L.O.T., Unit # 235684-5. A 38-year-old nulliparous obstetrical nurse was seen on referral because of inadequate control of adrenal hyperplasia while taking divided doses during the day. Some evidence of virilization probably was present at birth (clitoromegaly), though hirsutism did not become

manifest until after age 5. In 1954, the patient elsewhere underwent vaginoplasty, abdominal exploration, and clitoridectomy with the findings of follicular cyst of the ovary with occasional ova and a hypertrophic clitoris (5 cm.). The adrenals were thought normal to palpation. The patient was empirically treated with Premarin® and thyroid and had withdrawal bleeding. All therapy was discontinued in 1964, and she had spontaneous regular menses for one year with flow lasting 3–5 days and on occasion had associated cramping. Her baseline 17-KS were 51 mg. rising to 109 with ACTH and suppressing to 13.4 mg. with Decadron®. She was discharged on 25 mg. cortisone per day and was later changed to prednisone. However, she was seen on referral, and her urinary pregnanetriol was 31.5 mg/24 hrs. She was shaving twice daily. The patient was working swing shifts as a registered nurse. She was advised to take 5 mg. prednisone before going to bed and 2.5 on arising and an additional 2.5 mg during the day if necessary. Since institution of this therapy, her plasma testosterone has ranged from 16 to 28 ng% with concomitant loss of chest and arm hair, though facial shaving is still needed. Her plasma estradiol has been between 2 and 43 ng%, though she has remained anovulatory while cycling, as shown by plasma progesterones repeatedly less than 400 ng%. Her 17OH-P has ranged from 118 to 496 ng%.

Comment. Patients working swing shifts can experience considerable difficulty in controlling their excessive androgen production since the ACTH surge may come at a time when they are not receiving their larger dose of suppressive steroid. Also, changing shifts alter diurnal variation and may in itself be a stressful situation causing further decompensation. If even suppression is not obtained by giving a dose prior to anticipated ACTH surge, consideration of longer-acting injectable therapy such as utilized in infants may be considered. Neither this patient, nor our patient undergoing cesarean, had evidence of classical Stein-Leventhal type ovaries, although CAH has been noted associated with polycystic ovaries (40). The thickened capsules in such patients have been attributed to excessive androgens.

Patient P.B., Unit # 233484-2. A 23-year-old gravida II, para 1, abortus 0 had menarche at age 12 and cyclic menses until age 16 when she started skipping menses. At age 17, she had ovarian wedge resections elsewhere with diagnosis of Stein-Leventhal syndrome. However, menses did not resume. She was seen by another physician who treated her with prednisone. Menses then resumed, and the patient spontaneously achieved a pregnancy only to have mid-trimester loss with prolapsed cord, intrapartum death, and delivery by cesarean. On physical examination, the patient had considerable facial hirsutism, modest clitoromegaly, but normal size ovaries. The patient was again studied off therapy with elevated 17OH-P of 4.4 μg%. Her plasma progesterone was 132 ng%. With adequate suppression, plasma progesterone rose to 1.7 μg% (ovulatory level) and 17OH-P fell to 160 ng% (normal). The patient spontaneously resumed menses and became pregnant with last menstrual period November 11, 1974. On January 8, 1975, continuing the same dose of 5 mg prednisone at bedtime, her plasma testosterone was 80 and plasma 17OH-P 137 ng%, and her plasma progesterone was greater than 1.6 μg%.

Comment. Patients with congenital adrenal hyperplasia being adequately treated will be unable to have plasma or urinary estriols as an index of fetal well-being in as much as these steroids cross the placental barrier and suppress fetal-adrenal activity—a most important source of precursors for pregnancy estriol. Differential suppression tests should be able to delineate patients with primarily ovarian disorders as opposed to those with primarily adrenal disorders and prevent unnecessary wedge resections in the future.

Patient L.H., Unit # 235525-8. A 27-year-old patient was seen in consultation because she had developed Cushingoid features as a result of being on prednisone for persistent amenorrhea. Menarche was at age 12 with an average of one cycle per year until age 18 when she was placed on oral contraceptives with regular withdrawal bleeding for three years. Upon discontinuance, the patient remained amenorrheic for one year when she was seen by a gynecologist and had bilateral wedge resection of ovaries. She remained amenorrheic for another year except for scant spotting on rare occasion. The patient was admitted to another university center and underwent dexamethasone suppression test with 17-KS, suppressing from 21 mg/24 hours to 6 mg on the first day of high-dose dexamethasone. She also had adrenal and ovarian vein catheterization, showing adrenal venous plasma testosterones quite elevated with some elevation of ovarian and peripheral values. She was placed on prednisone 10 mg every other day with spontaneous menses occurring approximately every 6–7 weeks. She then relapsed into

amenorrhea. Medication was discontinued for retesting, and after one month off of therapy, her plasma 17OH-P was 1.8 μg% (approximately five to tenfold the normal values) with plasma testosterone 79 ng% (upper limits of normal for adult females in our laboratory are 60 ng%), plasma cortisol 10 μg% at 8 a.m., plasma estradiol 24.1 ng% (normal proliferative phase value), plasma progesterone 94.5 ng% (anovulatory value). On suppressive therapy, 17OH-P fell to 165 ng%, testosterone was 71 ng%, and plasma estradiol remained at 22.9 ng% with progesterone 78 ng%. Stimulation with Clomid®, escalating doses to a maximum of 150 mg/day times five days, indicates the patient remains anovulatory with progesterone 50.5 ng%, plasma estradiol 24 ng%, while 17OH-P has remained 112 to 216 ng% during the time she is being maintained on p.m. suppressive prednisone.

Comment. This patient with a mild form of 21-hydroxylation defect with first manifestations in postnatal period did not achieve smooth suppression with alternate-day therapy. Even though nighttime therapy has brought about normalization of 17OH-P and near normal values of plasma testosterone, she remains anovulatory and unresponsive to Clomid® at this time. In this patient, the elevation of 17OH-P in the plasma out of proportion to the progesterone would indicate that her primary pathway to 17OH-P is through 17-hydroxy-pregnenolone rather than through progesterone. Also, findings would suggest that even though near-optimal biochemical control of the disorder can be achieved, fertility does not automatically ensue. She probably needs further suppressive therapy. If optimum control is then achieved as shown by normal plasma testosterone, 17OH-P, and urinary 17-KS, then a search for other causes of amenorrhea are warranted, for they can be subject to such disorders as hypothalamic amenorrhea.

Patient J. L., Unit # 161059. An 11-year-old patient was seen in consultation after she had seen a group movie at school on sexual development in which a photograph of abnormal external genitalia was shown. She persisted in telling her teacher that she had such abnormal genitalia. Although "show and tell" in its fullest sense did not occur, this experience led to her being referred where the disorder was well characterized. She is now on suppressive therapy.

Comment. Clitoromegaly of this degree, had it been present at birth, surely would have been recognized, though possibly some physicians may attempt to downplay its importance. However, the clinical course of this patient, that is, the onset of hirsutism and facial acne just prior to her evaluation, would suggest postnatal onset of her disorder.

Patient C. G., Unit # 172230-1. A 20-year-old patient had onset of virilization at age 11, and the diagnosis of congenital adrenal hyperplasia was made at a medical university well known for its large series of congenital adrenal hyperplasia patients. Initial attempts to control her here by continuing cortisone acetate which had been instituted elsewhere failed, and she was switched to prednisone in 1970, taking 2.5 mg every eight hours. However, when seen in February, 1974, her 17OH-P was greater than 1.4 μg%, and her plasma progesterone greater than 1.6 μg%, with plasma testosterone 72 ng%. She was anovulatory as shown by endometrial biopsy and basal body temperature charts. Five mg. of prednisone at bedtime still failed to achieve suppression with plasma 17OH-P of 3.7 μg%, therefore, prednisone has been increased to 7.5 mg/day while sterility investigation is being pursued.

Discussion. Differential diagnosis of congenital adrenal hyperplasia includes disorders of adrenal and gonadal origin. Rarely are such entities as Morgagni-Stewart-Morel syndrome or Achard-Thiers syndrome of any importance in the differential diagnosis, if indeed they represent true syndromes.

Cushing's syndrome is readily differentiated by overnight dexamethasone suppression test in most patients and by baseline values of glucocorticoids. Rarely is virilization of the degree seen with CAH present in patients with Cushing's syndrome. Exogenous administration of virilizing hormones can present a problem particularly when the patient does not know what she has received. Anabolic steroids have been given in wasting diseases, osteoporosis, and to improve libido. The differentiation of ovarian hyperandrogenic syndromes including Stein-Leventhal syndrome can generally be made on the basis of differential suppression tests employing glucocorticoids to suppress the adrenal component and combination estrogen-progestogen preparation such as Enovid® E for the ovarian component (41, 42). True hermaphroditism usually is not much of a problem since prepubescent hirsutism is not usually evident even though ambiguous genitalia may exist. Steroid assays readily differentiate the conditions. Occasionally, patients with gonadal dysgenesis with a Y stem line (usually) may present with signs of hirsutism and clitoromegaly. This has been particularly

true of patients with gonadoblastomas or Teter's gonocytomas III and IV. Again, steroid assays readily differentiate the condition. In patients with virilizing ovarian tumors such as an arrhenoblastoma, elevated androgens will not suppress with exogenous administration of glucocorticoids. Further, their urinary 17-KS are generally not of the magnitude of those seen with CAH.

Summary. Enzymatic defects of adrenal and gonadal steroidogenesis have been described, many of which lead to amenorrhea and sexual ambiguity. Seven patients with congenital adrenal hyperplasia are presented who were first diagnosed at times far removed from the neonatal period. One such patient had dramatic onset of hirsutism, amenorrhea, and profound elevation of androgens. After suppression, she achieved two pregnancies, delivered, and subsequently has gone off therapy and continues to have cyclic menses in spite of borderline steroid values. The usefulness of a single nighttime long-acting glucocorticoid in achieving smooth suppression in patients with adrenal hyperplasia appears rational and is meeting with success. Diagnosis and monitoring of therapy of such patients has been facilitated by the availability of immunoassays for 17OH progesterone, and testosterone in lieu of urinary 17-KS, and urinary and plasma pregnanetriol assays.

Authors' note: Since preparation of this presentation, 5α reductase deficiency has been described in association with male pseudohermaphroditism. (Walsh et al, Familial incomplete male pseudohermaphroditism, type 2, decreased dihydrotestosterone formation in pseudovaginal perineoscrotal hypospadias, *N Engl J Med* 291:944–949, 1974).

Acknowledgment: The authors wish to thank Dr. Richard Horton for the testosterone antibody, Dr. Walter Wiest for the progesterone antibody, and Dr. V. B. Mahesh for the estradiol antibody.

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Treatment of Amenorrhea: When Pregnancy Is and Is Not Desired*

JOHN A. BOARD, M.D.

Professor of Obstetrics and Gynecology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

We have had three discussions this afternoon concerning amenorrhea, and most of these have dealt with the diagnosis of causative conditions. I am going to discuss the treatment of these women.

Whether or not the woman wishes to conceive in the immediate future determines the plan of treatment in most cases. If conception is desired, I believe it should not be immediately assumed that the amenorrhea is the sole cause of the infertility. I would check patency of fallopian tubes and adequacy of the husband's sperm production before treating for conception. Regardless of the plans for pregnancy, however, it should be determined whether the woman is merely not ovulating with adequate endogenous ovarian estrogen production or whether the ovulatory failure is associated with lack of estrogen as well. The former might occur if pituitary gonadotropins were reduced and/or the preovulatory LH surge were absent. The latter condition may be due to failure of production of pituitary gonadotropins or to menopause with elevated levels of pituitary gonadotropins.

Several brief case reports of women with amenorrhea will follow. In some of these, there will be organic disease of the extragenital endocrine glands such as the thyroid gland, or the adrenal gland, or the pituitary gland. In others, there will be no identifiable extragenital endocrine disease; then the treatment would vary depending on whether or not the woman wishes to become pregnant.

Case 1. This patient was a 35-year-old gravida 1, para 1, aborta 0 who was seen after having amenorrhea for six months. She had noticed tachycardia, sweats, and weight loss. The radioactive iodine uptake was 80% in 24 hours; this is much higher than normal for this laboratory. A diagnosis of hyperthyroidism was made. The patient was treated with radioactive iodine and had resumption of regular menses after the second course of treatment. She is not presently trying to become pregnant.

In preparing for this talk, I was looking for instances of thyroid disease that caused amenorrhea, and I couldn't find any where hypothyroidism was the etiologic factor. I am as aware as you all are of the thousands of women who have taken thyroid medication as treatment for amenorrhea, but in the patients' charts to which I had access, I could not find one where this was the real etiologic factor. I did find the following case of hyperthyroidism.

Case 2. This was a 30-year-old gravida II, para I who had had amenorrhea for two years after a spontaneous abortion. She had moderate hirsutism, but no other virilizing signs. An endometrial biopsy showed "resting endometrium," that is, proliferative glands without mitotic activity. Thyroid studies were normal, and two urinary 17-ketosteroid determinations were moderately elevated; 16.1 and 18.1 mg/24 hours. It was decided that this was a case of adrenal androgenic hyperfunction. The patient was initially treated with dexamethasone 2 mg three times a day for 2 days, followed by 0.75 mg/day for maintenance. Ultimately, this was reduced to 0.5 mg/day. Under this treatment, the urinary 17-ketosteroids fell to 2.7 mg/24 hours. Ovulatory cycles began and conception occurred.

* This is an edited transcription of a lecture presented by Dr. Board at the 46th Annual McGuire Lecture Series, December 5, 1974, at the Medical College of Virginia, Richmond.

Case 3. This was a 26-year-old gravida II, para 2 who was seen because of amenorrhea and galactorrhea since her last delivery two years earlier. This patient had been worked up about a year previously elsewhere and had had normal skull x-rays, normal visual fields, and normal EEG. The skull x-rays were repeated; this time a destructive lesion of the sella was seen, and the visual fields had a bilateral defect. A transsphenoidal removal of prolactin-producing pituitary adenoma was done leaving the remainder of the pituitary gland. Following this, spontaneous menses have returned and they are ovulatory. The visual fields have also returned to normal.

The first three cases dealt with patients who had organic diseases of extragenital endocrine glands. The remaining four cases have no identifiable extragenital endocrine disease.

Case 4. This was a 20-year-old gravida 0 whose menses began at age 13 and had occurred every 35 days lasting 7 days until two years earlier when amenorrhea had begun, coinciding with the first year of college. She had a history of having received thyroid medication in the past although she had received none for the preceding year. The free T_4 was 1.5 mg%, a normal value, and the maturation index was 0/65/35. Oral medroxyprogesterone was administered, and the patient had withdrawal bleeding after this. An extensive investigation was not done, but the medroxyprogesterone medication was continued for 3 months. After this, spontaneous cycles returned.

Patients who have endogenous estrogen can usually be treated with only a pure progestin given at monthly intervals. It is unlikely that they have anything seriously wrong with their hypothalamic-pituitary axis. When given an exogenous progestin at monthly intervals (we usually give medroxyprogesterone for 5 days beginning at cycle day 22), monthly bleeding episodes usually result. Some women who do not want to menstruate 13 times a year will be given the medication two to four times a year. I do not think it is good for endometrium to be continuously stimulated by estrogen, whether it is endogenous or exogenous, because of the possibility of endometrial hyperplasia, and I think that even if the woman is not enthusiastic about menstruating, she should be given this medication at least several times a year.

Case 5. This was an 18-year-old gravida 0 who had onset of menses at age 10 and who had had menses every 31 days lasting 5 days until she entered college. Prior to this, she had experienced amenorrhea in the summer when she had gone away to camp, but the amenorrhea had ceased when she returned home. She had very slight hirsutism, and there was no withdrawal bleeding after medroxyprogesterone. The serum FSH and LH were normal. Tests of thyroid function, skull x-rays, and urinary 17-ketosteroids were normal. The patient was treated with cyclic estrogens and progestins (conjugated estrogens 1.25 mg daily for 21 days with medroxyprogesterone 10 mg daily added on treatment days 17–21).

The failure of withdrawal bleeding after medroxyprogesterone alone in a patient who does have withdrawal bleeding after estrogen-priming before a progestin is given indicates lack of endogenous estrogen production. The group of patients without endogenous estrogen includes cases where the defect is ovarian (such as agenesis, castration, or premature menopause) as well as cases of pituitary failure (such as that secondary to defective releasing factors, ablation by surgery or radiation, and diseases such as Sheehan's syndrome). If this syndrome appears at a time when it is appropriate for a woman to stop menstruating, as would be the case if she were in her mid-40's, I don't think the condition necessarily needs to be treated. Certainly when it occurs in an 18-year-old girl, as this did, I believe that it is reasonable to treat with estrogen plus a progestin. This will result in regular episodes of withdrawal bleeding.

Case 6. This was a 27-year-old gravida I, para 1 who had become pregnant the first time without difficulty, but who had had amenorrhea for six years. She desired pregnancy. She weighed 208 pounds, had mild facial hirsutism, and normal adnexa. Urinary 17-ketosteroids were 4.4 mg/24 hours, a normal value. The maturation index was 0/86/14; a Rubin's test had shown tubal patency, and a postcoital test had shown abundant sperm. After medroxyprogesterone-induced withdrawal bleeding, this patient was given clomiphene 50 mg daily for 5 days, and she promptly became pregnant in the first month of treatment.

When clomiphene is used, the pregnancy rate will be around 30%. The incidence of ovulation is much greater than 30%, but every patient who shows evidence of ovulation does not always become pregnant. This may be due to the fact that we think the person is ovulating when she really is not. All of our

indices for detection of ovulation are based on the effects of progesterone, because we know that in normal women progesterone is present and exerts its effect primarily after ovulation, and we assume that this also happens in abnormal states. I am not absolutely sure that this is so, but I have no valid proof that it is not. Ovulation apparently is induced, or at least progesterone is produced, in about 70% of the women receiving clomiphene, but pregnancy occurs only in about 30%.

Sometimes couples will want to know when is the best time for exposure after clomiphene to achieve a pregnancy. It is my practice to tell the patients to begin having regular intercourse about four days after the last tablet and to continue this until the basal temperature has been up for three days. Clomiphene is not without side effects. Ovarian enlargement may occur in about 14% of patients, and sometimes the ovaries become quite large, but the problem is much less than with the agent that will be discussed shortly. Hot flashes are the common complaint that patients report. If patients are reassured about this and told that they are not menopausal, it does not seem to be a troublesome effect. The instance of multiple pregnancy is increased tenfold. Under normal circumstances, the incidence of multiple pregnancy is around 1 in 80; with clomiphene it will rise to around 1 in 10 or 1 in 12. Blurring of vision may occur in around 1% of patients, and when this occurs, it is an indication to discontinue the medication. Spontaneous abortion occurs at a higher rate than would be expected.

Case 7. This was a 29-year-old gravida 1, para 1, aborta 0 who desired pregnancy and who had had amenorrhea for nine months when she was first seen. She had been on oral contraceptive medication prior to her first pregnancy; this had been discontinued, and she had conceived promptly without difficulty. After that pregnancy, she took combination oral contraceptive tablets for several years. Her other workup had indicated that her thyroid function was normal, that the blood FSH and LH were normal, and that 17-ketosteroids were also normal. Tubal patency and sperm production were adequate. Attempts to induce ovulation with clomiphene began with a low dose of 50 mg daily for 5 days. This was raised gradually to 200 mg/day for 5 days, with chorionic gonadotropin added after this. This was not successful; then treatment with menopausal-chorionic gonadotropin was given according to the outline in Table 1.

TABLE 1
Outline of Gonadotropin Rx

Rx Day	Cervical Mucus	Plasma Estradiol	Rx
1	0		HMG 75-75 u.
2	0		HMG 150-150 u.
3	0		HMG 150-150 u.
4	1+		HMG 150-150 u.
5	1+	134 pg/ml	HMG 150-150 u.
6	2+	179 pg/ml	HMG 225-225 u.
7	2+	237 pg/ml	HMG 300-300 u.
8	3+	332 pg/ml	HMG 300-300 u.
9	3+	478 pg/ml	HMG 300-300 u.
10	4+	938 pg/ml	HMG 10,000 u.
11			
12	BBT down		
13	Sustained rise in BBT began, followed by menses.		

In such cases, one may get response to menopausal plus chorionic gonadotropin. The instance of pregnancy with this treatment is around 25%. This treatment is also associated with side effects. One has to be very careful in giving it. Ovarian enlargement may occur in up to 20% of the cases, and in extreme instances may be associated with acites and even plural effusions. The cysts may rupture, and there may be hemoperitoneum. The severe hyperstimulation syndrome is found to be associated with abdominal distention and hemoconcentration (because so much of the body's total fluid volume has gone into the abdominal cavity). The treatment is bedrest, intravenous fluids with close monitoring of electrolytes, and avoidance of pelvic examinations. This can become serious, can lead to thrombosis, and there have been several deaths. The instance of multiple pregnancy with menopausal-chorionic gonadotropin treatment is 20–37%, and the instance of abortion is around 28%; an incidence greater than would be expected with normal spontaneous ovulation. In one series, it was found that three-fourths of the multiple pregnancies were twins, and one-fourth of the multiple pregnancies were three or more.

There are several problems in treating women with gonadotropins. One wants to give enough medication to induce ovulation, but not so much that the hyperstimulation syndrome is produced. In this particular patient, the menopausal gonadotropin dosage was gradually increased until day 10 when good cervical mucus was seen, indicating that, more than likely, enough medication had been

given. Laboratory tests of estrogen production were done to determine that too much had not been given. In many institutions, the determination is of urinary estrogen, but at the Medical College of Virginia there is a technique whereby plasma estradiol can be measured in about six hours. The patients have blood drawn in the morning and return at 4:00 p.m., at which time the laboratory data is available. The aim is to reach a level of between 500 and 1000 pg/ml of estradiol. If the level stays under 1000 pg/ml, the incidence of hyperstimulation syndrome is much less than if the level is higher. If this patient had been given another day of treatment, a situation might have been created where hyperstimulation would have occurred. The patient did not become pregnant, although evidence for ovulation was obtained from basal temperature charts. I want to emphasize this because I think this is a way a physician can get in trouble. One can decide when he has given enough estrogen by the effect on cervical mucus, but one cannot tell when he has given too much. If estradiol levels are too high, one would not give chorionic gonadotropin, stop the treatment, and try again in a month or so, giving less medication. I think to avoid serious complications in treating a nonlethal condition, there has to be some way of assessing the estrogen production from the stimulated ovaries.

I have tried to illustrate the treatment for amenorrhea of different causes and to emphasize the fact that the treatment is different when the woman wishes or does not wish to become pregnant. I have also pointed out some of the hazards of the various methods of treatment of this condition.

Patient Factors Limiting Success of Cancer Detection*

DEAN R. GOPLERUD, M.D.

Associate Professor of Obstetrics and Gynecology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

The American College of Obstetricians and Gynecologists has established as one of its goals for the next decade the reduction of mortality from breast and pelvic cancer by 50% (1). Radiation therapy and surgery are the main modalities of treatment for most genital cancers. These modalities have advanced to the level of diminishing returns. Immunotherapy is in its infancy, and chemotherapy is presently used mainly for palliation and for prolongation of life except for a few malignancies, choriocarcinoma being the classic example.

Barring a monumental breakthrough, it appears that any major advance in improving mortality statistics will be the result of early cancer detection. Cancer detection involves many factors, but basic units in the scheme include the patient, the physician or his representative, and the facility in which detection procedures are carried out. It is safe to assume that most people do not need to be convinced that early cancer detection is a desirable goal. Many facilities exist such as physicians' offices, hospital facilities, and public clinics, all of which can figure prominently in cancer detection. One of the major unfulfilled objectives of cancer detection programs is the inclusion of all eligible patients. This requires motivation of patients in such a manner that they will seek out and utilize the available cancer detection facilities.

The Papanicolaou smear and routine pelvic examination have been shown repeatedly to be simple, reliable, painless, and widely available. Yet, only an estimated 50% of the eligible women in our community have ever had a Pap smear. There is an even higher proportion of post-menopausal women who have never had a Pap smear. It is precisely from this population that we see patients who have far-advanced tumors of the cervix at the time of their first admission.

What are the reasons for this apparent discrepancy between the availability of the means for early detection and the lack of utilization? This is the problem I would like to explore and make some suggestions for improvement.

If women are to participate in programs for early detection of cancer, there are several steps that must be taken. First, they must know about the program and its value. The dissemination of cancer information is a worthwhile endeavor, but education of the patient takes place in different ways. Certainly the cancer education program of the American Cancer Society, our public health agencies, our medical societies, and universities should not be abandoned, but to a great extent we are preaching to the "already converted." The women's clubs and PTA groups that often sponsor education programs by the local Cancer Society are composed largely of women who are already convinced of the value of early cancer detection. Most gynecologists in private practice are very concientious about performing regular pelvic examinations including Pap smears on their patients. Commendable as this may be, the number of positive smears obtained in this manner is not great, and occasionally one may wonder if it is worth the effort and expense to do smears once or twice a year on women who have had several previously negative examinations. Asymptomatic women who come regu-

* Presented by Dr. Goplerud at the 46th Annual McGuire Lecture Series, December 6, 1974, at the Medical College of Virginia, Richmond.

larly to the private gynecologist's office are basically a low-risk group for the development of cervical cancer.

One of the proven ways to screen patients is to combine screening procedures with services that the patients need and want. Mature women are either in the child-bearing years or post menopausal. We need to look at these groups separately.

The sexually active young woman is likely to be seen in a private office or a public clinic for either contraception or prenatal care. At that time she is very likely to have a Pap smear and pelvic examination done; in fact, it would be difficult for her to avoid it. Consequently, these patients have cancer-screening tests done as an ancillary service, not because this is their primary motivation for seeking care. In order to continue to get the care she wants, this type of patient is given return appointments and will have repeat examinations and smears done.

If these young, sexually active women have an abnormal smear, follow-up examination is usually recommended. Consequently, the patients referred to our Anaplasia Clinic are most commonly drawn from this group. It is not difficult to do effective cancer screening if you are providing a service that patients desire and will seek out.

The post-menopausal woman of 65 who comes in bleeding from a Stage III-b cancer of the cervix does not fall into any of the categories related to pregnancy. All too often she gives a history of having her last encounter with a physician at the time of her last delivery some 30 or more years previously. Why don't these patients come in for examination? We must examine the motivation and understanding of the medically-indigent, middle-aged, and post-menopausal woman, since this is the group that has the greatest need for cancer screening and also shows the poorest utilization of cancer-screening services.

Sociologists tell us that motivation in medically-indigent patients is related to many factors (2, 3). Fear of surgery, fear of cancer, and ultimately, fear of death are important. The pressing problems of immediate day-to-day life such as obtaining sufficient food, clothing, and adequate shelter often preclude concern for a possible future problem which could be prevented by such measures as cancer screening. Lack of knowledge about the availability of screening procedures and their possible significance is important, but although patients often are aware at some level of these measures, they still do not take action. If patients are to be convinced that they should seek medical care when they do not have symptoms, they must be made aware that the disease in question can affect them. They must also be convinced that the disease is curable and prevention is better than treatment for the active disease, even though cure is likely.

One of the common reasons given for not seeking a Pap smear is that the patient feels well and equates the lack of symptoms with good health. Most patients in this age group are aware that cancer-screening examinations are available. However, some patients are afraid that if cancer is found, an operation may be recommended. In one survey, many of the patients interviewed felt that cancer was essentially incurable and therefore there was little to be gained by finding out the bad news earlier than necessary. Other patients feel that the test may be painful or that they will be subjected to indignities in a clinic situation. Fear that surgery will cause some interference with sexual function is a common concern. These beliefs and attitudes have been found consistently in ghetto populations by numerous surveys (3).

The woman who is asymptomatic must first learn about the availability of cancer screening. The commonly used mass media such as radio, television, and the press are not particularly effective in reaching the ghetto population which is at highest risk. These women are more often influenced by personal contact with friends and relatives and by their own personal experiences in health facilities (3).

The patient should then be made aware that she is a possible candidate for the development of cancer. Subsequently, she must be convinced that treatment is effective and that she could benefit from such treatment if it were necessary.

Utilization of services will be improved if the clinic facilities are located in areas close to where the patients live. Convenient hours must be arranged. This often means having clinics open in the evening.

Finally, let us consider the woman who has symptoms which might logically suggest the possibility of cancer but who delays seeking care. We have recently attempted to interview some of the patients who were admitted with cancers which obviously have been present for long periods of time in an effort to learn more about the reasons why the delays occurred.* Fear of learning the diagnosis and fear of the

* (Oral communications from J. Jones, R. N., Department of Nursing, Medical College of Virginia Hospital, Richmond, Virginia).

consequences of treatment rank high on the list of reasons for patient delay. One nulliparous patient stated, "I think if I had had a baby I would almost have had to go to a doctor then, and maybe I would have continued to go after that. I guess I just have always been scared to go to the doctor because of what he might find." At this point the patient described some of her relatives who had died from malignant disease. She went on to say, "My friends and neighbors have been after me for a long time to have an examination and so had my doctor. I have been going to see him every three months for blood pressure examination. He would offer to do a pelvic examination each time I would go for my yearly physical, but I would say no. My friend had told me how painful the exam was and I would get nervous when I went to the doctor. He was young and I just didn't feel right. He would examine me otherwise and I always had no problems. It is all my fault. If only I had listened to my friends and my doctor."

Another example is that of a patient who had bleeding for many months before seeking medical attention. This patient was a very religious woman who felt that her faith would heal her and probably interpreted the presence of symptoms as some sort of punishment. The patient stated, "When your time comes to die, you must go. If the Lord had taken me two weeks ago I would have been ready." There is a fatalistic attitude here as well as religious fervor.

Interestingly enough, the patient underwent surgery with complete removal of all visible tumor. She had an uneventful recovery and was assured that she had a good prognosis. In spite of the outcome and the long delay on her part, she was very reluctant to give any credit to the people who cared for her in the hospital.

In the 1974 edition of its Manual of Standards for Obstetrics and Gynecologic Services in Accredited Hospitals, the American College of Obstetricians and Gynecologists makes the following recommendation. "Good medical practice clearly warrants the establishment of cytologic screening as a hospital routine. It is therefore recommended that regardless of the service to which she is admitted, every female hospital patient who is age 18 or over or is sexually active should have a pelvic examination and a cervical-vaginal cytologic smear unless a negative smear has been recorded within a year. To implement this program, it is essential that hospitals make smears readily available and make every effort to encourage their routine use."

Along this same line, there are now three states, New York, Illinois, and Hawaii, that have passed legislation making the Pap smear mandatory for all women who are admitted to the hospital who fit into the categories outlined in the ACOG recommendations (4). It seems likely that similar legislation may be forthcoming in other states. There is no reason why departments of obstetrics and gynecology in any given hospital cannot exert pressure on the hospital administration and the rest of the medical staff to incorporate requirements such as these in their hospital bylaws. Certainly a voluntary action of this type would be more acceptable to most physicians than to have it forced upon them by legislative decree.

The question immediately arises as to who shall perform these Papanicolaou smears on women who are admitted to services other than Gynecology. The nurse practitioner programs which are developing in several medical centers may provide one answer to this problem. A number of hospitals have employed such individuals to do routine Pap smears on all female admissions with good patient acceptance and good results. Any patient is given the opportunity to refuse to have a smear performed if she has some personal objection. In addition, any woman who has had a smear performed by her private physician within the year prior to admission is not required to have a smear done provided the cytology was negative (4).

A program of this kind would not solve the entire problem, but it could be a significant step in the right direction. Patients admitted to hospitals constitute the captive population that is most accessible and the one over which we as physicians have the most control.

Summary. Patient education is an important part of preventive measures and is most likely to be effective when provided in a health-related setting. Cancer-screening services are best utilized when they are combined with other health services that the patient needs or desires. Convenience of health services such as location of clinics, convenient hours, and the attitude of health workers are significant factors. Captive populations such as hospitalized patients, inmates of institutions, individuals who must take employment physical examinations, etc., may be utilized to achieve more complete screening of the population at risk. The influence of friends,

neighbors, and relatives can not be overestimated. Efforts must be made to utilize these influences in a positive way. Finally, all physicians are urged to push for routine Pap smears on female hospital admissions as a voluntary program in their own hospitals.

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Radical Hysterectomy for Carcinoma of the Cervix*

JOHN J. MIKUTA, M.D.

Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Hospital of the University of Pennsylvania School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Radical hysterectomy refers to the removal of the uterus and cervix and, in addition, to the removal of the upper one-half to one-third of the vagina, the parametria and the pelvic lymph nodes. This operation, which is commonly called the Wertheim operation, was actually first described by Clark in the United States and Ries in Germany. Wertheim's original operation for carcinoma of the cervix consisted only of a partial parametrial removal and removal of the upper one-third of the vagina. It did not include pelvic lymphadenectomy or the removal of the lateral portions of the parametria.

The early efforts at radical hysterectomy for cervical cancer resulted in operative and surgical mortality in the range of 25–75%. In 1903, when it became obvious that radiation therapy, available then only in the form of radium, was effective for the control of cervical cancer, clinicians abandoned the radical hysterectomy procedure in favor of this limited form of radiation. A few individuals persisted in performing the operation, and in 1935, the British gynecologist and surgeon, Victor Bonney, reported on 500 consecutive patients on whom he had done radical hysterectomy. His operative mortality was 16%.

In 1939, Dr. Joseph Meigs of Boston decided to take a second look at the radical hysterectomy procedure in view of some of the technical advances which had occurred in medicine, primarily in the areas of blood transfusion, anesthesia, antibacterial chemotherapy, and improvement in pre and postoperative care. Between 1939 and 1951, Meigs performed 100 consecutive radical hysterectomy operations without a single surgical mortality. This astounding feat provided the impetus in the United States for a revision of thinking about this procedure in the post-World War II era.

Meigs also defined the advantages of utilizing radical hysterectomy in preference to radiation therapy for cervical cancer. These are as follows:

1. There can be no tumor recurrence in the cervix itself.
2. There can be no new tumor growths in the cervix or upper vagina.
3. The problem of radio-resistant tumors is avoided.
4. There can be no radiation injuries to the bowel or the bladder.

In addition to the advantages listed by Meigs, two other important factors can be considered as helpful. The first of these is the ability to preserve ovarian function in young women. The incidence of metastasis to the ovary in a patient with early carcinoma of the cervix is negligible, and it is possible, by using radical surgery to preserve at least one ovary, to avoid the onset of the climacteric. The second aspect is that the gynecologic oncologist will know the extent of the disease as reported to him by the pathologist after thorough study of the removed specimen. From this not only will the prognosis be known but also additional therapy can be considered.

Also, there are several clinical situations in which, given equally available expert radiation

* Presented by Dr. Mikuta at the 46th Annual McGuire Lecture Series, December 6, 1974, at the Medical College of Virginia, Richmond.

therapy and radical pelvic surgery personnel and facilities, one might elect a radical hysterectomy approach. These are as follows:

1. Previous pelvic surgery (supravaginal or total hysterectomy)
2. Presence of adnexal mass or masses, or previous pelvic inflammatory disease
3. Diabetes mellitus
4. Pregnancy
5. Radiophobia

Appreciating what has already been stated with regard to the advantages as well as the indications for the use of radical hysterectomy and pelvic lymphadenectomy, there are three significant limiting features:

1. *The medical condition of the patient.* This is primarily related to the patient's general condition, her age, obesity, and the presence of underlying cardiovascular and other diseases which might influence the development of significant operative and postoperative complications.

2. *The type and extent of the malignancy which is being treated.* In cervical carcinoma, one of the limiting factors is the extent of the disease and the degree of its parametrial infiltration. From a clinical standpoint, cancers of the cervix favorable for a radical hysterectomy are clinical Stage I-a, minimal to moderate-sized lesions which are I-b, or very early Stage II-a or Stage II-b tumors. More extensive local disease increases the probability of inadequate surgery as well as the risk of cutting through the tumor at the time of operation. Similarly, the presence of any tumor which is spread beyond the pelvic area in the abdomen, particularly lymphatic involvement of the para-aortic nodes or liver, is considered a contraindication to radical hysterectomy approach as is the finding of any distant metastasis during the preoperative oncologic evaluation. Finally, radical hysterectomy may be utilized in patients who have minimal, central, post-radiation recurrence in which the lesion has not extended to the bladder and rectum. This operation, under proper circumstances, is preferable to the more extensive and complicated procedure of pelvic exenteration.

3. *The availability of a surgeon to perform radical hysterectomy.* This factor in general provides the greatest limitation to the surgical approach, since during the standard gynecologic residency program, there is neither the time nor the experience available in the performance of radical pelvic surgery for the resident to develop the necessary skills. Similarly, in the routine practice of gynecology, a physician will not have sufficient numbers of such patients to maintain his operative expertise and capability. This limitation is gradually being overcome by the development of training programs in gynecologic oncology which include training in the performance of radical pelvic procedures. The identification and utilization of the gynecologic oncologist who can perform such procedures and who limits his area of specialization to the treatment of gynecologic cancer and its problems, is now a reality. A certifying board in gynecologic oncology has been developed and individuals are being recognized for skill in this particular area. In addition, training programs are now available throughout the country for individuals already qualified in obstetrics and gynecology. They can receive additional training for two years to develop these skills.

Let us turn to some of the improvements which have occurred in the results with radical hysterectomy in the management of cervical carcinoma. As mentioned earlier, the operative and surgical mortality was one of the major limiting factors in this procedure. Since Meigs' original series, other writers in recent times have reported series of patients on whom radical hysterectomy was carried out with minimal mortality. The inevitable catastrophe will occur from time to time when the surgeon, at times overstepping the bounds of good judgement, undertakes radical pelvic surgery on a patient and has an unfavorable result. In general, the operative and surgical mortality should be in the range of 0.5%.

Scrupulous attention must be given to the thorough preoperative evaluation of the patient, not only from the standpoint of her disease process so that an operation of this type will not be attempted on a patient with distant metastatic disease, but also attention must be given to the general physical condition of the patient, primarily her cardiovascular, pulmonary, and renal systems. Infection of the urinary system must be brought under control prior to surgery. The operation itself must be meticulously carried out with the knowledge of the extent of the operation, the patient's condition, and possible complicating factors well known to a competent medical anesthesiologist. Careful dissection of the pelvis with specific care around the large vessels and ureters will insure a much lower incidence of significant vascular and urinary tract complications which are the chief intra-operative problems. Finally,

careful attention to the details of postoperative care are essential to avoid the problems associated with pulmonary, bowel, and urinary areas and to reduce the incidence of thromboembolic phenomena in these patients. For more detailed descriptions of these areas of importance in the pre and postoperative care, one's attention is directed to Nelson's *Atlas of Radical Pelvic Surgery*.*

The major problem creating morbidity with radical hysterectomy for cervical carcinoma is associated with the urinary tract. While Meigs listed among the advantages of radical hysterectomy the avoidance of radiation complications to the bowel and bladder, it became evident that there was a significant morbidity associated with these structures from radical hysterectomy. In reviewing all of the complications associated with radical hysterectomy at the Hospital of the University of Pennsylvania, in an unselected group of radical hysterectomy procedures, the greatest number, almost 50%, had complications associated with urinary tract. These were chiefly urinary tract infections, ureteral and vesical fistulas, and postoperative bladder dysfunction.

Let us look specifically at the problem of uretero-vaginal fistula. The incidence of uretero-vaginal fistula as reported by Meigs varied from 10 to 15%. A significant improvement in the uretero-vaginal fistula rate was reported by Green, who found that the incidence of this complication could be reduced to approximately 4% by leaving the urethral catheter in the bladder for a minimum of 6 weeks following the operation. It was felt that this maneuver kept the ureteral bed in a more stable position and allowed better healing and vascularization. In 1966, Green also described a technique of ureteral suspension in which the ureter is approximated by several sutures to the superior vesical artery from the origin of this vessel to the ureterovesical junction. In his original report, he found only one fistula in 65 patients. This experience has been repeated in other centers, and it has been substantiated as an effective and simple method of reducing the uretero-vaginal fistula rate. This complication instead of being in the range of 10 to 15%, is now reported in the range of 1 to 2%.

Rather than keeping the uretheral catheter in position in the bladder for a long period of time, it has been the practice at the Hospital of the University of Pennsylvania to evaluate the bladder prior to and after operation by the use of cystometry. A baseline measurement of bladder function is obtained prior to surgery, and, on approximately day 9 or 10 following surgery, a repeat cystometric evaluation is carried out. Frequently the bladder will be found to be of the autonomous neurogenic type, where there is absence of the sensation of filling as well as failure of the bladder to accommodate to filling. If attention is not paid to this alteration in vesical function, the result will be overdistention and overflow incontinence. Generally by the 10th to 20th day after surgery there will be a gradual return of function toward normal, first with the return of the sensation of filling and the desire to void, and later a correction of the detrusor function where accommodation to filling and maintainance of low pressures develop until the patient has the proper desire to void.

Other aspects aimed at reducing urinary tract morbidity are the reduction of infection and the avoidance of trauma. There must be clearance of preoperative urinary infection, gentle and minimal handling of the ureter during the procedure, with an effort to preserve its blood supply as much as possible, and finally pre and postoperative administration of appropriate systemic antibiotics. Local intravesical antibiotics may be utilized through a triple-lumen Foley catheter (Neosporin® G-U irrigant). Another approach is to carry out the suprapubic drainage technique to reduce possible contamination of the bladder seen so often with the use of the urethral catheter.

An added factor in reduction of uretero-vaginal fistula is the use of techniques to reduce the collection of serum and lymph in the retroperitoneal space. This was originally described by the Chinese using the paracoccygeal route. More recently, Welch, Pratt, and Symmonds applied closed-suction techniques to the retroperitoneal area via the abdominal wall. This

TABLE 1
Cancer of Cervix 1955–1969 Radical Hysterectomy Stage of Disease

Stage I-a	28
Stage I-b	62
Stage II-a	8
Stage II-b	4
Total	102

* James Nelson, Jr., *Atlas of Radical Pelvic Surgery*, Appleton, New York, 1969.

TABLE 2
Radical Hysterectomy 5-yr. survival
Cancer of Cervix HUP 1955–1969

	Total	L	%
Stage I	90	75	83.3
Stage II	12	8	66.6

decreases the amount of materials which might become infected, reduces the possibility of lymphocyst formation, and also may improve the ability of the ureter to maintain its blood supply. The results associated with radical hysterectomy as primary treatment for cervical cancer at the Hospital of the University of Pennsylvania are noted in Tables 1, 2, 3, and 4. Comparison of statistics from one institution to another regarding the operable stages of cervical cancer show that radiation and surgery can provide approximately the same 5-year survival. The surgical proponents have always had the advantage, especially where absolute survival figures are considered, since the surgical patients are always better selected, usually in better medical condition, and more likely to survive five years.

Finally, it is important to consider some areas for the future with regard to radical hysterectomy in the management of cervical carcinoma. First, the use of cytological vaginal screening is providing the gynecologic oncologist with younger patients who have an earlier disease to treat. These patients are very favorable surgical candidates. Second, there is an unanswered question regarding the management of patients who are found at radical hysterectomy to have pelvic lymph nodes involved with tumor. Presently most of these patients are receiving postoperative irradiation therapy to the pelvis. The advisability of combining radical surgery with radical radiation must not only be measured in survival results but also in terms of the seriousness of the complications that frequently follow such combined therapy. Third, one might question the advisability of

TABLE 3
Cancer of Cervix HUP 1955–1969
Radical Hysterectomy–All Cases

	Total	L	%
Stage I-a	28	24*	85.7
Stage I-b	62	51*	82.3
Stage II-a	8	4	50.0
Stage II-b	4	4	100.0

* one patient each group lost—considered dead

TABLE 4
Cancer of Cervix HUP 1955–1969 (5-yr. survival)

Stage	Negative nodes L	%	Positive nodes L	%
I-a	24/27*	88.8	0/1	0
I-b	45/50*	90.0	6/12	50.0
II-a	3/4	75.0	1/4	25.0
II-b	2/2	100.0	2/2	100.0

* one patient in each group lost—considered dead

abandoning the procedure when para-aortic lymph nodes are found to be involved with tumor. The question which needs to be answered is whether such patients are better handled by carrying out the radical hysterectomy procedure, where technically feasible, and then adding pelvis and para-aortic irradiation postoperatively. Answers to the second and third problems need to be obtained, and this probably can best be accomplished through national cooperative study groups.

Finally, if cervical cancer detection programs continue to increase the findings of preinvasive malignancy, with the eradication of invasive cervical cancer, one wonders whether the case load will be sufficient for the maintainance of large numbers of experts in radical pelvic surgery among gynecologic oncologists. Only time will answer this question.

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Abstracts of Papers Presented at the 46th Annual McGuire Lecture Series

Medical College of Virginia, Richmond, December 5–6, 1974.

Control of Endometrial Cancer

SAUL B. GUSBERG, M.D., D.SC.
Professor and Chairman, Department of Obstetrics and Gynecology, Mount Sinai Medical School, New York, New York

Epidemiologic studies of this disease may offer etiologic clues and help us recognize high-risk factors. Of special interest in this respect is the infrequency of endometrial cancer in Asian women and the increase in its incidence in migrants to Western countries.

The definition of high-risk factors in the perimenopausal years and the possibility of screening them by ambulatory aspiration curettage could offer the possibility of prophylactic measures that could interrupt the progression to invasive cancer. The recognition of endometrial cancer precursors, especially adenomatous hyperplasia, is critical in such surveillance and can lead to control in the same manner that the diagnosis of cervix cancer precursors has contributed to the steady decline in mortality from that disease.

Modern steroid metabolic technology has enabled us to gain significant insights into the problems of hormone sensitivity of endometrial cancer and offers promise of allowing us to make real therapeutic advances in this area. The recognition of adrenal androstenedione as the postmenopausal estrogen precursor and the techniques of quantifying estradiol receptor sites in target cells will be very important in these studies.

The Diagnosis and Management of Cervical Intraepithelial Neoplasia

RICHARD T. UPTON, CAPT MC USN
Chairman, Department of Obstetrics and Gynecology, Naval Regional Medical Center, Portsmouth, Virginia

Carcinoma of the uterine cervix continues to be a major health problem to the women of this country. In order to reduce the morbidity and mortality from this preventable problem, it is important that we develop and utilize effective techniques of early diagnosis and treatment of the disease in its intraepithelial stage.

For more than two decades the Papanicolaou cytosmear technique has been available to clinicians as a screening test for cervical neoplasia. For many years the indicated follow-up evaluation of abnormal Papanicolaou smears suggesting cervical neoplasia was to perform a cold-knife conization biopsy of the cervix of these patients with abnormal cytosmears. With the increasing acceptance in recent years of the colposcope as an adjunctive diagnostic tool, it is now possible for most clinicians to perform, or have performed on their patients with abnormal cervical cytosmears, a thorough colposcopic examination of the cervix and vagina and to obtain directed biopsies from areas of abnormality as indicated by direct, magnified vision. Examination of the endocervical canal by direct vision so far as possible and by endocervical curettage in each case are important procedures in the proper evaluation of these patients. By these careful adjunctive diagnostic techniques, it is possible to definitively diagnose the degree and extent of virtually all cervical intraepithelial neoplastic processes.

In the absence of neoplastic changes in the endocervical curettings, those patients with biopsy diagnosis of varying grades of intraepithelial neoplasia are then managed according to the age of the patient and the severity of the dysplastic process. The patients with mild or moderate dysplastic changes are treated with cervical cryotherapy using either freon or nitrous oxide delivered by any of several currently available and acceptable machines. Upwards of 90% of these early dysplastic changes can be reversed or eradicated by this technique. For those patients with more advanced grades of dysplasia or carcinoma in situ, management should take into consideration their reproductive interests. Those who have no further desire for pregnancy may be managed by hysterectomy with preservation of normal ovaries. If conservation of childbearing capability is desired, then treatment with cryotherapy or therapeutic cold-knife conization followed by careful cytologic and colposcopic evaluation is in order. The pregnant patient with cervical intraepithelial neoplasia may be managed with careful colposcopic delineation of the magnitude and extent of the neoplastic lesion, visualization of 360° of normal endocervical epithelium, and assurance that the biopsy was taken from the most abnormal area of the cervix. The pregnancy may then be maintained without

further therapy or diagnostic efforts, vaginal delivery accomplished, and then careful follow-up and definitive management in the postpartum period carried out.

For those patients with endocervical curettings containing evidence of dysplasia or carcinoma in situ and/or with cervical biopsies reported as invasive carcinoma, definitive management appropriate to the patient and the staging is then carried out *without* conization. For those patients with evidence of dysplasia or carcinoma in situ in the endocervical curettings but with the biopsy diagnosis of cervical intraepithelial neoplasia, and those patients in whom endocervical curettings could not be obtained, a cold-knife conization is indicated. This may then be followed immediately after definitive diagnosis, either the same day or within 48 hours, by definitive management as indicated by the stage of the neoplastic disease.

Many techniques have been used over the years for the treatment of cervical intraepithelial neoplastic processes. These include the use of varying degrees of surgical excision, radiation therapy, ultrasound, and extremes of temperature by either cauterization or freezing techniques. In recent months, the use of the Carbon Dioxide Surgical Laser has come under investigation as a possible means of colposcopically directed, precise, laser surgical excision of the areas of cervical epithelial abnormality. This technique offers considerable promise, and the preliminary studies are being prepared for presentation in the near future.

The effectiveness of these forms of management, as briefly discussed above, are dependent upon the cooperativeness of the patient to obtain periodic health evaluations, the alertness and willingness of clinicians to obtain at least annual cervical cytosmears on their female patients, and the increasing availability of the trained colposcopist to define and refine the adjunctive diagnostic techniques and precise management that more appropriately fit the patient's needs as dictated by the degree of her neoplastic process.

Breast: Non-Cancerous Diseases

JUNE 29–JULY 3, 1976 STRASBOURG

4TH INTERNATIONAL SYMPOSIUM ON SENOLOGY

European Association of Radiology (E.A.R.)

I. STUDY GROUPS
(Invited lectures, Discussions)

A. Investigation Methods

Physical examination, Diaphanoscopy, Radiography, Thermography, Echography

Cytology, Histology

Biochemistry, Endocrinology

Psychology, Computer analysis

B. Mastopathies

Cystic mastopathies, Galactorrhea, Discharges, . . .

Fibroadenoma, Adenosis, Fibrosis, Involutive States, . . .

Pre-cancerous Diseases: Dysplasia, Phyllodes, Non-invading Carcinomas, . . .

C. Lactation

Maternal Suckling

Pathology, Psychology, Sociology

II. COMMUNICATION, CONFERENCES

a. Topics of Study Groups A, B, C

b. Infections, Traumatisms, Infarcts, Lipoma, Necrosis, Thrombophlebitis, . . .
Pathology of Skin, Aerola, Nipple.

c. Malformations, Ungracefulness, Amazonism, . . .
Plastic Surgery

d. Breast Pathology in Man, Androgyny

(Continued on page 51)

after taking a potent analgesic 360 times in 3 months...

after taking a potent analgesic 360 times in 3 months...

how big a dose will now bring relief if it is a narcotic?

"Tolerance is an ever-present hazard to continued use of narcotics.... The very first dose diminishes the effects of subsequent doses."[1] And, as increasing amounts of narcotics are required to control pain, distressing adverse effects—lethargy, hypotension, constipation, etc.—can needlessly debilitate the patient.

1.Sadove, M. S.: A look at narcotic and non-narcotic analgesics, *Postgrad. Med.* 49:102, June 1971.

how big a dose will now bring relief if it is Talwin®?

Chances are, the same 50 mg. Talwin Tablet you prescribe originally will continue to provide good pain relief. Talwin can be compared to codeine in analgesic efficacy: one 50 mg. tablet appears equivalent in analgesic effect to 60 mg. (1 gr.) of codeine. However, patients receiving Talwin Tablets for prolonged periods face fewer of the consequences you've come to expect with narcotics. There should be fewer "adverse effects" on her way of life.

Tolerance rare: Tolerance to the analgesic effect of Talwin Tablets is rare.

Dependence rare: *During three years of wide clinical use, there have been a few reports of dependence and of withdrawal symptoms with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.*

*In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.**

Generally well tolerated by most patients*: Infrequently causes decrease in blood pressure or tachycardia; rarely causes respiratory depression or urinary retention; seldom causes diarrhea or constipation. Acute, transient CNS effects, described in product information on following page, have occurred in rare instances following the use of Talwin Tablets. If dizziness, lightheadedness, nausea or vomiting are encountered, these effects may decrease or disappear after the first few doses.

*See important product information on next page for adverse reactions, patient selection, prescribing and precautionary recommendations.

in chronic pain of moderate to severe intensity

Talwin® 50 mg. Tablets

brand of

pentazocine

(as hydrochloride)

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in chronic pain of moderate to severe intensity

Talwin® 50 mg. Tablets

brand of

pentazocine

(as hydrochloride)

in chronic pain of moderate to severe intensity

Talwin® Tablets brand of pentazocine (as hydrochloride)
Analgesic for Oral Use

Indication: For the relief of moderate to severe pain.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Drug Dependence. There have been instances of psychological and physical dependence on parenteral Talwin in patients with a history of drug abuse and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in withdrawal symptoms. There have been a few reports of dependence and of withdrawal symptoms with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.*

In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under 12 years of age is limited, administration of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* Although respiratory depression has rarely been reported after oral administration of Talwin, the drug should be administered with caution to patients with respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Decreased metabolism of the drug by the liver in extensive liver disease may predispose to accentuation of side effects. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no causal and effect relationship has been established.

Adverse Reactions: Reactions reported after oral administration of Talwin include *gastrointestinal:* nausea, vomiting; infrequently constipation; and rarely abdominal distress, anorexia, diarrhea. *CNS effects:* dizziness, lightheadedness, sedation, euphoria, headache; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, hallucinations (see *Acute CNS Manifestations* under **WARNINGS**); and rarely tremor, irritability, excitement, tinnitus. *Autonomic:* sweating; infrequently flushing; and rarely chills. *Allergic:* infrequently rash; and rarely urticaria, edema of the face. *Cardiovascular:* infrequently decrease in blood pressure, tachycardia. *Hematologic:* rarely depression of white blood cells (especially granulocytes), usually reversible and usually associated with diseases or other drugs which are known to cause such changes, moderate transient eosinophilia. *Other:* rarely respiratory depression, urinary retention, toxic epidermal necrolysis.

Dosage and Administration: *Adults.* The usual initial adult dose is 1 tablet (50 mg.) every three or four hours. This may be increased to 2 tablets (100 mg.) when needed. Total daily dosage should not exceed 600 mg.

When antiinflammatory or antipyretic effects are desired in addition to analgesia, aspirin can be administered concomitantly with Talwin.

Children Under 12 Years of Age. Since clinical experience in children under 12 years of age is limited, administration of Talwin in this age group is not recommended.

Duration of Therapy. Patients with chronic pain who have received Talwin orally for prolonged periods have not experienced withdrawal symptoms even when administration was abruptly discontinued (see WARNINGS). No tolerance to the analgesic effect has been observed. Laboratory tests of blood and urine and of liver and kidney function have revealed no significant abnormalities after prolonged administration of Talwin.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition. *Treatment.* Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

How Supplied: Tablets, peach color, scored. Each tablet contains Talwin (brand of pentazocine) as hydrochloride equivalent to 50 mg. base. Bottles of 100.

Winthrop Laboratories, New York, N.Y. 10016 Winthrop

50 mg. Tablets

Talwin®

brand of

pentazocine (as hydrochloride) (1623M

(*Continued from page 47*)

e. Computer Analysis, Nomenclatures, Codifications,

f. Comparative Psychology, Veterinary Art, Ethology

g. Breast Functions (maternity, sexuality, aesthetics): arts, literature, fashion, history, . . .

h. Miscellaneous

III. POST-UNIVERSITY TEACHING

(Pre-Symposium Meetings on techniques and all applications)

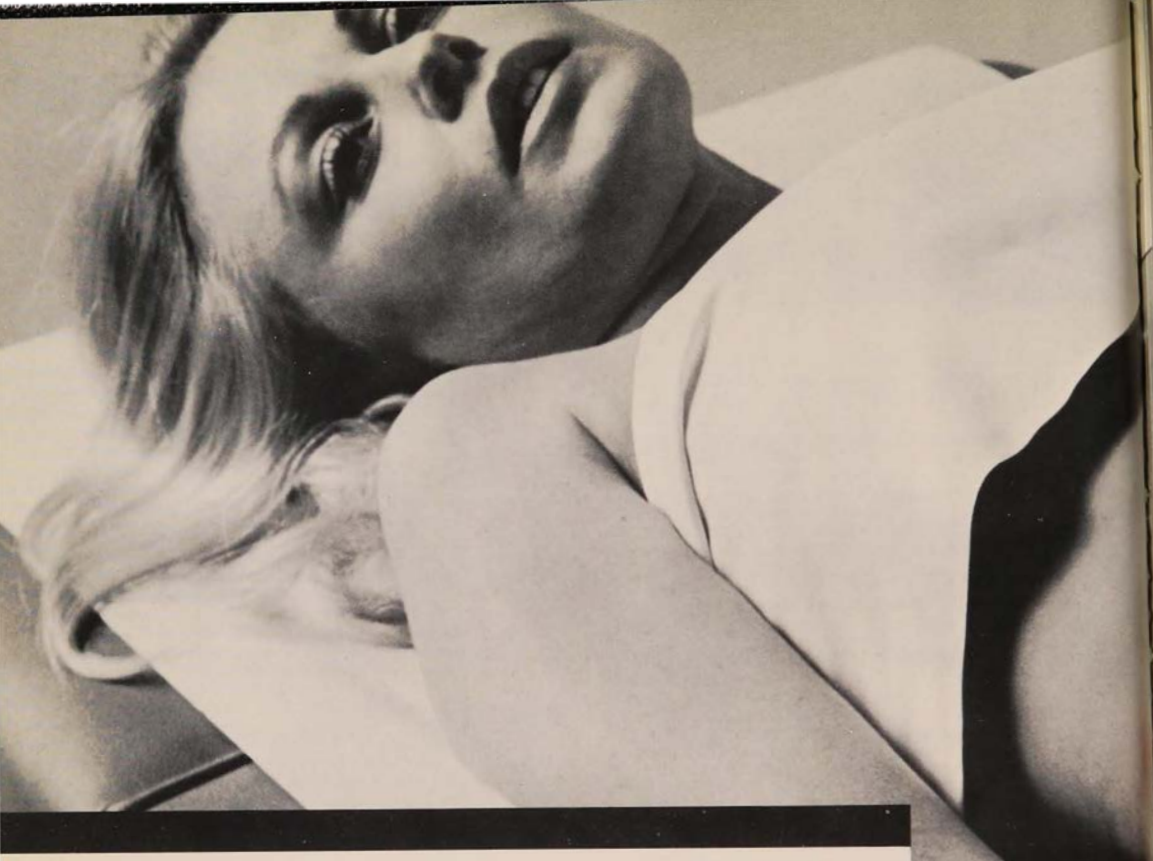
1. Journées Nationales on ECHOGRAPHY
   (French Society of Echography)
   June 28–29, 1976
2. Post-University Courses on THERMOGRAPHY
   (European Association of Thermography)
   June 28, 1976
3. Post-University Courses on XEROGRAPHY
   June 28, 1976

IV. SCIENTIFIC EXHIBITION

V. TECHNICAL EXHIBITION

Simultaneous Translation: English, French, and German, in all rooms.
Program and Information:

SYMPOSIUM SEIN 1976—PROF. CH. GROS
PALAIS DES CONGRÉS
67 STRASBOURG-FRANCE



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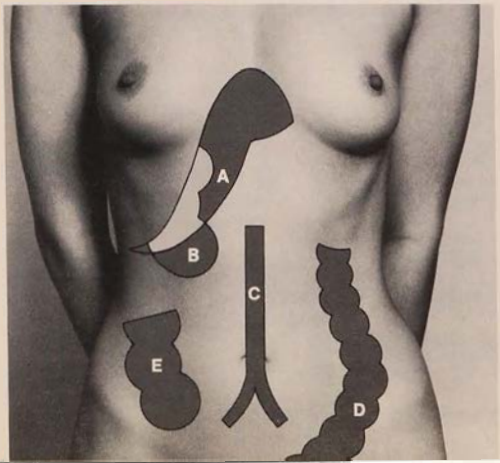
Normally palpable organs: the edge of the liver descending, on inspiration, below the costal margin (A); the lower pole of the right kidney (B), the abdominal aorta (C); the descending colon and the sigmoid (D); the ascending colon (E); and occasionally the bladder (though rising of this organ beyond the pubis does not necessarily indicate disease).

Impossible to outline, unless diseased, distended or enlarged: the gallbladder, pancreas, stomach, small intestine, transverse colon and spleen.



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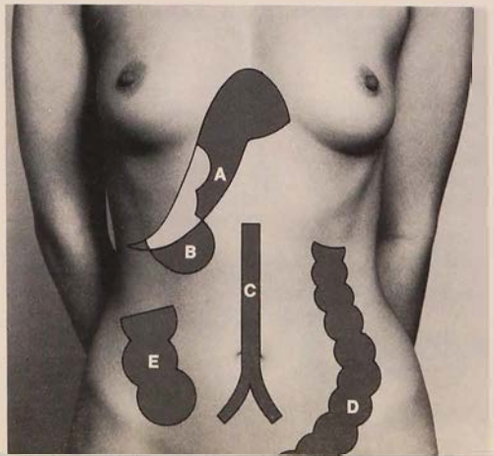
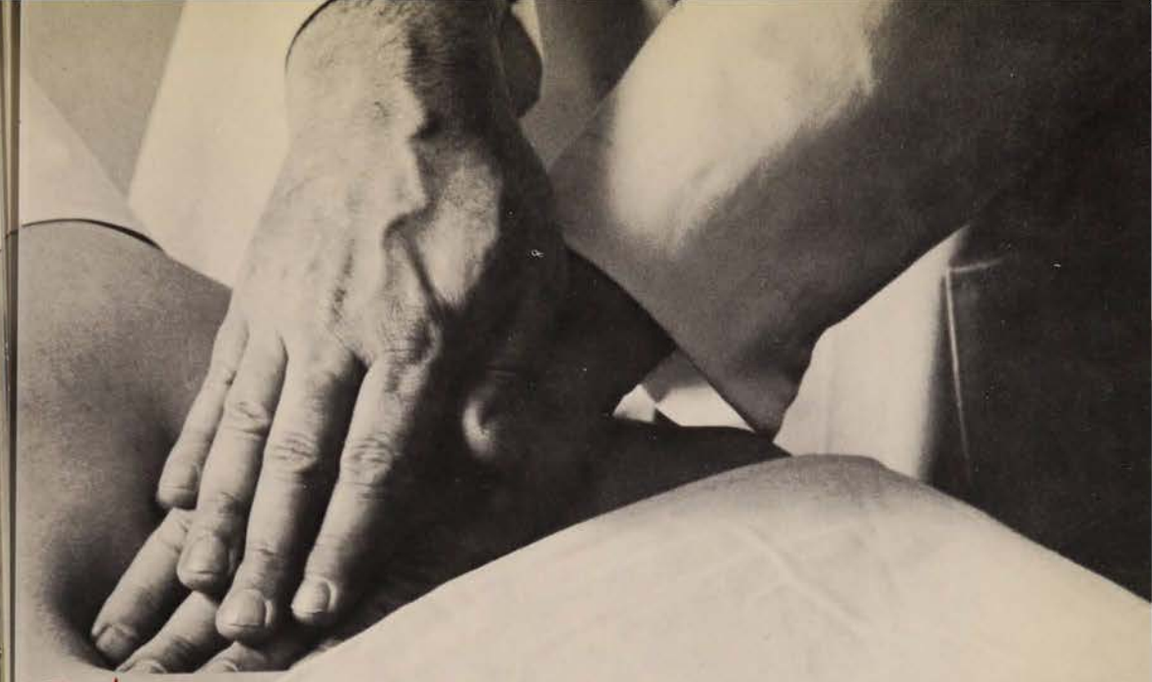
Normally palpable organs: the edge of the liver descending, on inspiration, below the costal margin (A); the lower pole of the right kidney (B), the abdominal aorta (C); the descending colon and the sigmoid (D); the ascending colon (E); and occasionally the bladder (though rising of this organ beyond the pubis does not necessarily indicate disease)

Impossible to outline, unless diseased, distended or enlarged: the gallbladder, pancreas, stomach, small intestine, transverse colon and spleen



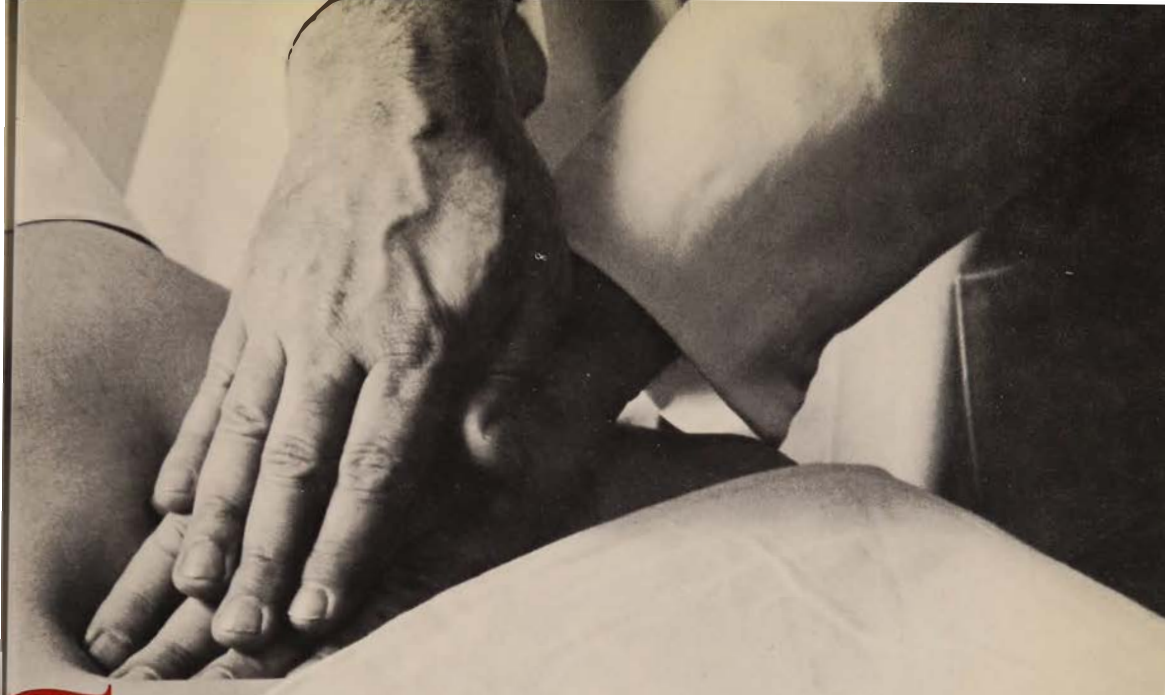


Spasm reactor? Donnatal®!

	each tablet, capsule or 5 cc teaspoonful of elixir (23% alcohol)	each Donnatal No. 2	each Extentab
amine sulfate	0.1037 mg	0.1037 mg	0.3111 mg
e sulfate	0.0194 mg	0.0194 mg	0.0582 mg
ne hydrobromide	0.0065 mg	0.0065 mg.	0.0195 mg
arbital	(¼ gr.) 16.2 mg	(½ gr.) 32.4 mg	(¾ gr.) 48.6 mg
g. may be habit forming)			

Brief summary. Adverse Reactions: Blurring of vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur on higher dosage levels, rarely on usual dosage. Contraindications: Glaucoma; renal or hepatic disease, obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy), or hypersensitivity to any of the ingredients.

A·H·ROBINS A. H. Robins Company, Richmond, Virginia 23220



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Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states, somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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Roche Laboratories
Division of Hoffmann-La Roche Inc
Nutley, N.J. 07110

If there's good reason to prescribe for psychic tension...

When, for example, despite counseling, tension and anxiety continue to produce distressing somatic symptoms

Prompt action is a good reason to consider Valium® (diazepam)

2-mg, 5-mg, 10-mg tablets