Chapter 12
MALFORMATIONS

The growth of an organ may be arrested, or it may develop normally and then degenerate, or it may develop in an abnormal way. In any case there results a malformation. Most genital deformities are due to partial arrest of development, and to understand them it is necessary to have clearly in mind the way in which the organs develop.

POINTS IN DEVELOPMENT

The first structures indicative of the genitourinary organs are the **wolffian ducts,** which appear in the embryo about the fifteenth day, and the **wolffian bodies,** which appear on the eighteenth day. These structures represent the future kidneys and genital apparatus. They lie on each side of the median line.

During the fourth week another duct appears near the wolffian body on each side. These are the **müllerian ducts.** The wolffian ducts go to form the excretory ducts of the genital apparatus in the male. The müllerian ducts go to form the excretory ducts of the genital apparatus in the female. A part of the wolffian body of each side finally forms the genital gland of that side, i.e., the ovary in the female and the testicle in the male.

At the end of the first month the middle part of each wolffian body shows thickening and proliferation, resulting in the formation of elevated bands called "genital ridges." These are the earliest traces of the genital glands. For a few days they remain indifferent. Very soon, however, a difference in the two sexes is noticed. The primitive female gland "possesses a large number of the primitive sexual cells and evidences a tendency of its elements to arrange themselves into groups, in which the large primitive ova become central figures." The primitive male gland, on the other hand, shows a tendency to the formation of a network of cell cords—the forerunners of the seminiferous tubules. "Microscopic examination of the sexual primitive glands even at the end of the fifth week is capable of distinguishing the future sex of the being." In a short time there is a difference in the gross appearance of the gland, with a difference in the arrangement of the ducts.

The parts played by the wolffian ducts and müllerian ducts differ in the two sexes. In the **female** the müllerian ducts are the most important. The lower portions of the ducts of Müller become fused and form the vagina and uterus, and the upper portions remain separated and form the fallopian tubes (Figs. 921 to 923). The lower end of the vagina is formed from the

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urogenital sinus. Later the septum which separates the upper portion from this lower portion (hymen) breaks down so that the vagina is open. If this septum fails to disappear, an imperforate hymen results. The very end of the other extremity of the müllerian duct is usually represented by a miniature cyst attached to one of the fimbria and called the "hydatid of Morgagni."

The wolffian body forms the ovary and also contributes the transverse tubules of the parovarium. The upper part of the wolffian duct remains as the "head tube" of the parovarium. The lower part of the wolffian duct sometimes remains in whole or in part, and is then known as "Gartner's duct" (Figs. 42 and 43). These parovarium tubules are all atrophic structures of but little importance. The ovary is the important organ formed from the wolffian body in the female.

In the **male** the wolffian tubules and wolffian duct contribute the important system of excretory tubes represented by the vas deferens and the epididymis, while the müllerian duct is atrophic, its ends alone remaining. Its outer end forms the "hydatid of Morgagni," closely connected with the epididymis, and its inner end forms the "sinus pocularis," or "uterus masculinus," opening into the prostatic portion of the urethra.

External Genitals (Fig. 924). "Until the ninth or tenth weeks the external genitals afford no positive information as to sex"—they are indifferent. They then begin to differentiate and "usually by the end of the third month the external sexual organs are characteristic beyond doubt." Up to the sixth week the external openings of the intestine and of the urinary apparatus are received within a common cloacal recess whose rectourogenital orifice is surmounted by a small conical elevation, the "genital tubercle." The lower and posterior surface of the genital tubercle is divided by a furrow—the "genital groove"—bounded by thickened edges called the "genital folds." Gradually a septum develops, separating the rectal opening from the genitourinary opening. The "genital tubercle" forms the **clitoris** and the "genital folds" form the **labia.**

The **vestibule** is formed by the cloaca or common opening of the intestinal tract and urinary tract in the early embryo. The **perineum,** developing, separates the rectum from this common vestibule. And the septum (hymen) closing the end of the rudimentary vagina (fused müllerian ducts) breaks allowing the vagina to open into the vestibule. This opening through the septum varies much in size, shape, and situation, giving the various forms of opening found in the hymen. It is usually small, and roughly crescentic in shape.

The **vagina** is formed by the fusion of the lower portions of the two müllerian ducts and the absorption of the longitudinal septum between the cavities. The lower one-fifth of the vagina is formed from the urogenital sinus. The **uterus** is formed by the fusion of the middle portions of the two müllerian ducts and the absorption of the septum between the cavities. The **fallopian** tube of each side is formed by the upper portion of the müllerian duct of that side. The **ovary** of each side is formed from a portion of the wolffian body of that side. The **parovarium** consists of the "transverse tubules," which are formed from the wolffian body, and the "head tube," which

Fig. 921.

Fig. 922.

Fig. 923.

Figs. 921, 922, and 923.—Development of the genital organs. Diagrams illustrating the transformation of an indifferent primitive genital system into the definite female and male types. (Modified from Arey, after Thompson: Developmental Anatomy.)

is formed from the wolffian duct. The **paroophoron,** lying in the broad liga-
ment near the parovarium, is the atrophic remains of the lower segment of
the wolffian body. For an excellent review of the embryology of sexual struc-
ture and hermaphroditism, the reader is referred to an article by Greene.
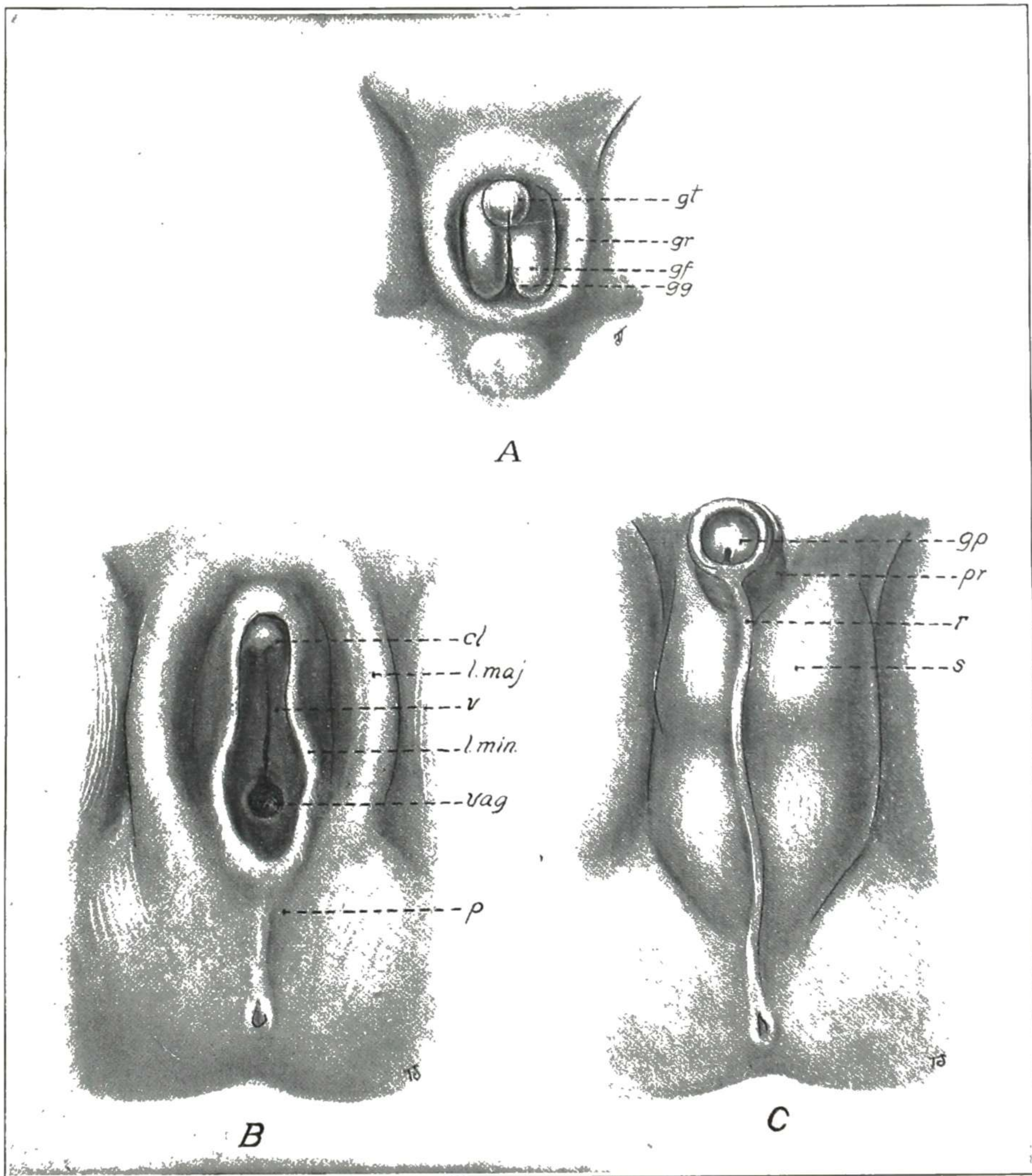
Fig. 924.—Development of external genitals (after Ecker-Ziegler models). *A,* Indif-
ferent stage (eighth week) ; *gt,* genital tubercle ; *gr,* genital ridge ; *gf,* gential fold ; *gg,* genital
groove. *B,* Female type ; *cl,* clitoris ; *l. maj.,* labia majora ; *v,* vestibule ; *l. min.,* labia minora ;
vag., vagina ; *p,* perineum. *C,* Male type ; *gp,* glans penis ; *pr,* prepuce ; *r,* raphe ; *s,* scrotum.

ANOMALIES OF DEVELOPMENT

In recent years through research in various fields our knowledge of the
causes of developmental pathology has been integrated so that the origin of
the various abnormalities are better understood. It is known that changes in
the environment of the embryo, whether chemicals, hormones, viruses, x-rays,
or alteration in temperature, can cause abnormalities of many kinds. The type

of abnormality is somewhat dependent upon the stage of development at which the environmental factors are altered. Among tissues of the same histologic type, portions which are growing rapidly are more severely damaged than are others which are quiescent. Gruenwald, in an excellent review of developmental pathology, points out that, though these abnormalities are largely concerned with the embryo, some measure of development goes on in the postnatal life and these disturbances do not differ essentially from those occurring prenatally. That the genetic factors are of prime importance is evidenced by the fact that inherited abnormalities are reproduced as are normal traits.
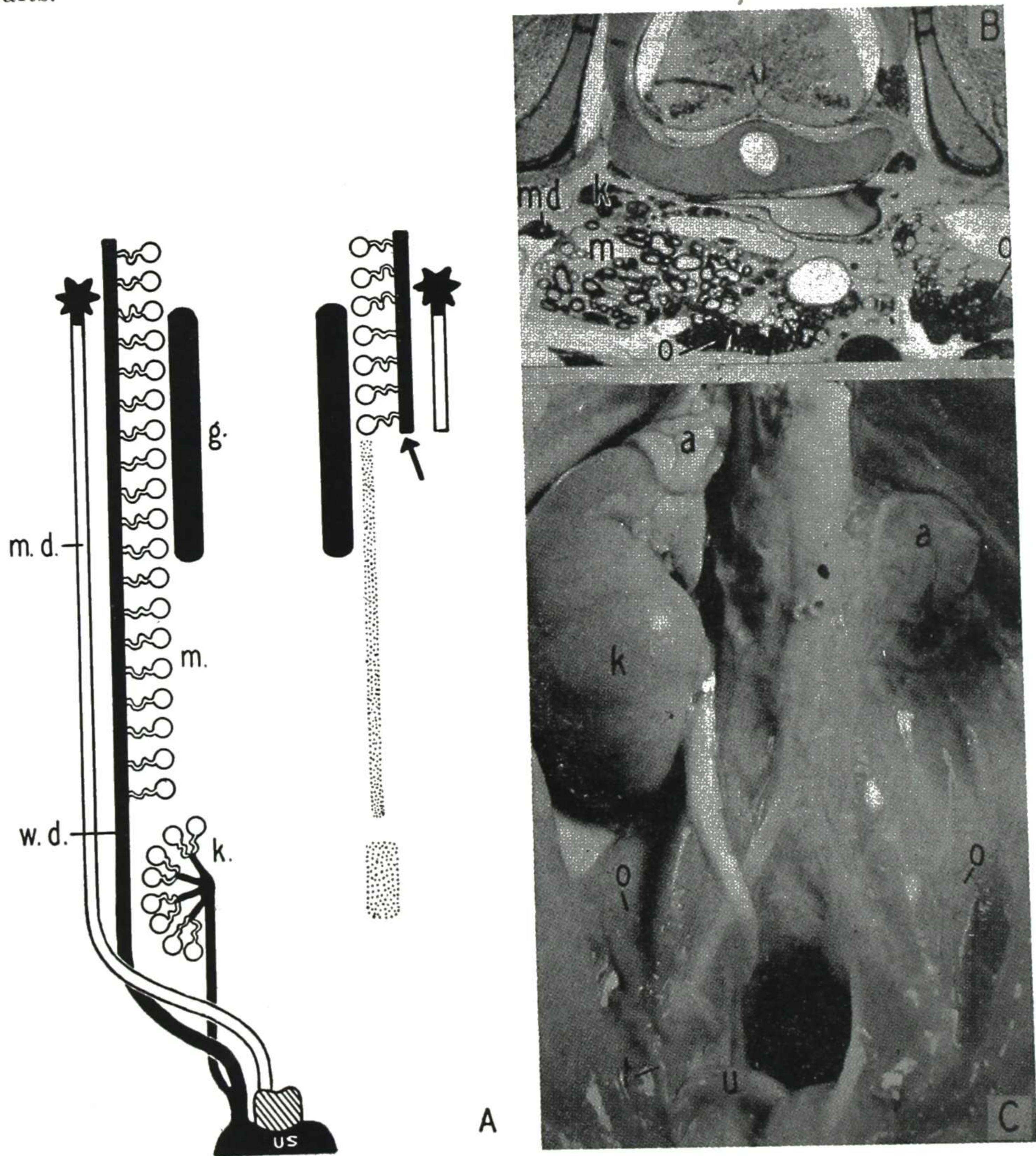

Fig. 925.—One primary abnormality causing a syndrome of malformations by dependent development. The diagram (*A*) shows on the left side the urogenital organs of the embryo developing normally. The parts which develop independent of others are shown solid black; those which depend on these parts are outlined. The right side of the diagram shows the multiple effects of termination of growth of the Wolffian duct at the arrow. All other defects are sequelae of this event. This can be done experimentally in chick embryos by destruction of the growing end of the duct. The result is shown in *B*. The corresponding human malformation in female infant is shown in *C*. *a*, Adrenal; *g*, gonad (ovary or testis); *k*, kidney; *m*, mesonephros; *m d*, müllerian duct; *o*, ovary; *t*, tube; *u*, uterus; *u s*, urogenital sinus; *w d*, wolffian duct. (From Gruenwald: Am. J. Obst. & Gynec., July, 1949.)

In malformations, just as in normally developing organs, the development of one portion depends in many cases on the development of adjacent or component parts; hence the abnormalities in development may extend far beyond local area of damage. In a chick embryo, if the growing end of the wolffian duct is destroyed in a minute area, not only does the entire duct fail to develop from that point on, but the other organs dependent upon it for their development will also be absent (see Fig. 925). This explains the frequent association of abnormalities of the urinary tract with abnormalities in the genital development.

The factors influencing sexual differentiation have been summarized in a monograph by Carl R. Moore; his conclusions are: "The most acceptable evidence for control of sex differentiation in vertebrates rests upon the conception of the operation of genetic sex-differentiating factors unconnected with sex hormone actions. The production of intersexual or hermaphroditic conditions is believed to be dependent upon nonhormonal genetic factors in the combination of which male determiners or female determiners have failed to establish clear dominance. In some cases gene mutations may be involved. The intersexual conditions are not believed to rest upon a hormonal basis for their origin, but when atypical reproductive structures are produced or are retained from any cause, they will respond to sex hormones when they become available."

TYPES OF ANOMALIES

The more common anomalies of development are as follows:

1. A septum is found between the vaginal cavity and the urogenital sinus, constituting **imperforate hymen** (Figs. 926 and 927).

2. More rarely, perfect canalization does not take place in the fused müllerian cords (each of which develops a central canal and becomes a müllerian duct), resulting in a closed place at some point in the canal, giving **atresia of vagina** (Figs. 928 to 934) or atresia of cervix. In very rare cases all of the lower fused cords fail to canalize, causing **absence of vagina** (Fig. 935).

3. The septum between the two fused müllerian ducts may persist all the way to the hymen, in which case there exists **double vagina** (Figs. 936 and 937).

4. The vagina may open into the urethra instead of into the urogenital vestibule. This gives the anomaly shown in Figs. 938 to 941.

5. The septum may persist into the uterine portion of the müllerian tract, forming a uterus septus.

6. The middle portions of the müllerian ducts may fail to fuse, giving a double uterus (uterus didelphys).

7. They may fuse only imperfectly, giving a uterus with rudimentary horns. There may be either two well-marked horns (uterus bicornis), or a fairly well-developed uterus with one rudimentary horn, as shown in the illustrations.

8. The wolffian duct may persist in some extent, giving a duct lying alongside the vagina called Gartner's duct (Figs. 42 and 43). This may extend all the way along the vagina and open near the hymen, or there may be only remnants of the tube here and there. These remnants sometimes develop so as to form small vaginal cysts. Such cysts are situated in the vaginal wall

along the course of the atrophic wolffian duct. This duct extends through a portion of the uterine wall, and a uterine tumor may arise from it.

The above mentioned are the principal gross developmental anomalies ordinarily met with (Fig. 942). See also classification under Anomalies of the Uterus. There are many other rarer anomalies, of which lack of space prevents mention. These vary in each organ all the way from slight modification to complete absence. The **ovary** is probably the least frequently affected by anomalies, and yet, as rare as they are, they have produced many surprises in abdominal work, especially in the cases of pregnancy following the supposed complete removal of both ovaries. This means, of course, that some ovarian tissue remains, and it is usually said to be a "third ovary." While the development of three normal ovaries is not impossible, the condition present in the cases under consideration is, as a rule, "lobulation" of the ovary
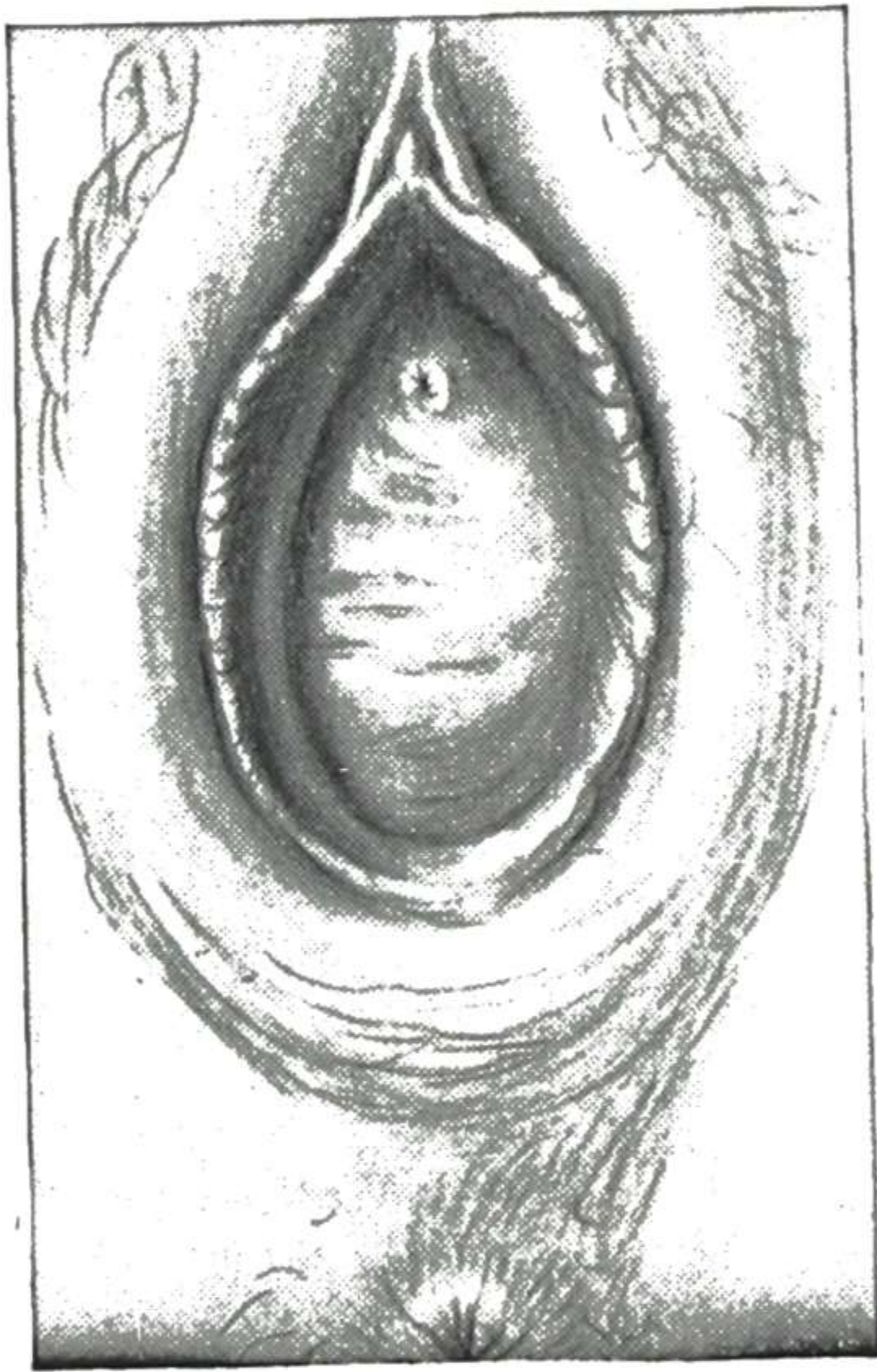
Fig. 926.

Fig. 927.

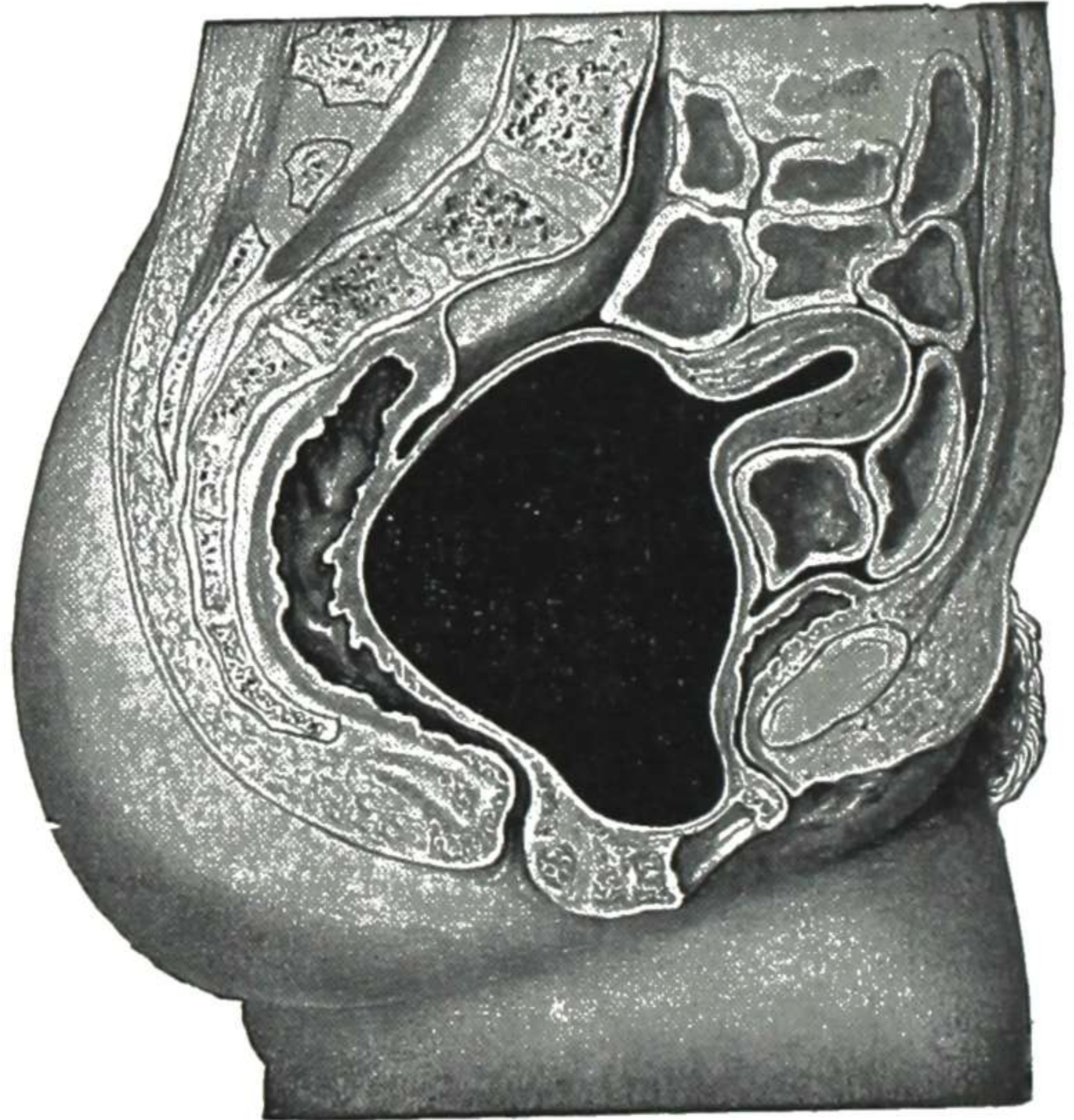Fig. 926.—Imperforate hymen. There is no vaginal opening, the urethra being the only opening present in the vestibule.

Fig. 927.—Hematocolpos, which may result from imperforate hymen or from atresia at the lower portion of the vagina. The menstrual blood has not yet distended the uterus.

(From Montgomery: Practical Gynecology.)

of one or both sides, and not the presence of a complete third ovary. The lobulated ovary may show only a marked constriction, or it may be divided into two or three or many separate lobules, with considerable space between various lobules. Bovée mentions a case of his in which the ovary of each side was represented simply by numerous small particles of ovarian tissue scattered over a large area of the posterior surface of the broad ligament, and resembling verrucal excrescences. It is evident that in such a case some outlying nodules of ovarian tissue would almost certainly be missed, especially if obscured by an inflammatory exudate.

The malformations most commonly requiring treatment are:

Imperforate Hymen.   Vagina Opens Into Urethra.
Atresia of Vagina.   Malformations of Uterus.
Double Vagina.   Pseudohermaphroditism.

Imperforate Hymen

If the time-honored supposition that the hymen is simply the remains of the septum between the embryonic vagina and the sinus urogenitalis is true, then imperforate hymen means the failure of this septum to break down. If, on the other hand, the hymen represents another structure formed by active circular proliferation just back of the septum area, then imperforate hymen or occluded hymen is the result of excessive proliferation and coalescence, instead of failure to break down. Taussig has investigated this subject embryologically and in two articles presents substantial points in favor of the proliferation theory.

Imperforate or occluded hymen causes no disturbance until puberty. After puberty there is a collection of menstrual blood back of the imperforate hymen (Fig. 927). This gradually increases in amount and distends the vagina. If the obstruction is not relieved, there is gradual dilation of the uterus and even of the fallopian tubes, forming a cystic mass, the content of which is blood and the walls of which are formed by the vagina and uterus.

The **symptoms** are characteristic. At the age of puberty no menstruation appears, but about every four weeks the patient feels ill, with pain in the lower abdomen and the usual disturbances accompanying menstruation. The mother supposes that the girl is going to menstruate, but there is no flow. This is repeated month after month. As the collection of blood increases, the pain and disturbance become more marked, the patient's health begins to suffer, and a tender mass appears in the lower abdomen. Finally the patient becomes so sick that the physician makes a local examination. He finds that there is no vaginal opening, but instead there is a fluctuating mass occupying the position of the vagina and uterus (Fig. 927).

The **treatment** is crucial incision of the distended hymen, and, if the membrane is thick, excision of most of it. The cavity above should be washed out with normal saline solution and then an antiseptic solution such as 1 per cent neutral acriflavine in glycerin, or a sulfa cream should be instilled until the danger of infection is past. In the past, death occasionally occurred from extension of infection to the peritoneum.

Tompkins reported a series of five cases of imperforate hymen with hematocolpos and collected 113 from the literature, and presented a study of diagnosis and treatment.

Atresia of Vagina, Absence of Vagina

The method of origin of this malformation has been explained. The condition may vary all the way from a thin septum blocking the canal to complete absence of the canal. The external genitals may be normal.

The serious conditions which may result from simple atresia of the vagina, and the importance of early investigation of symptoms, such as amenorrhea and slight recurring abdominal pains, are demonstrated in the following case of ours:

Miss D., aged twenty-three years, was referred for operation for pelvic tumor. Examination showed a tender mass filling the central pelvis and a mass on each side extending into the lower abdomen. The upper limits could not be outlined on account of the deep location and tenderness. The patient had a temperature of 104° F. and was in a serious condition. On vaginal examination an obstruction was found just inside the vaginal opening, and there was a bloody discharge mixed with pus. The history was somewhat uncertain and there

were other factors that made diagnosis of intrapelvic conditions difficult, but facts were eventually established to warrant a diagnosis of the following sequence of events.

The patient had atresia of the vagina near the outlet, as indicated in Fig. 928. After puberty there was a slow accumulation of menstrual blood back of the obstruction, as indicated in Figs. 929 to 932. There had been no menstruation. She had had abdominal pains off and on, and on going over the matter she thought they had been worse about once a month for several months past. Apparently they were never very severe.

About a month previous to her admission to the hospital a slight bloody discharge appeared. Apparently the pressure of the accumulating blood had gradually stretched the thin membrane occluding the vagina so much so as to cause a small opening through which came the slight bloody flow, as shown in Fig. 933. This flow continued for a week or so and then the patient became suddenly very ill, with high fever.

Bacteria eventually propagated in this bloody culture medium, followed up the stream into the mass of old blood, and then multiplied rapidly, forming an abscess involving the distended vagina and uterus and tubes, as indicated in Fig. 934.

The plan of treatment was to drain from below. This might prove sufficient, and the anesthesia and vaginal work would permit deeper examination for confirming or disproving the diagnosis made. There was of course the possibility that the diagnosis was erroneous and that the large masses above were tumors, with degeneration or suppuration or twisted pedicle. The vaginal drainage improved conditions temporarily and the information obtained tended to confirm the diagnosis of genital tract distended with blood and infected.

In three days the temperature became high again, there was no diminution in the size of the lateral masses, and it was evident that abdominal operation was necessary in spite of the danger it involved. At the abdominal operation the tubes were found enormously distended, pushing up the sigmoid and the cecum. The distended tubes and uterus were removed and extensive drainage was established. Examination of the distended tubal specimens showed them filled with a mixture of pus and old blood. The patient had a stormy time, but eventually recovered.

On making the vaginal **examination,** an obstruction is met with at some point in the vagina. If there is a collection of menstrual blood back of the septum, fluctuation may be detected. Digital examination per rectum will give some idea of the extent of the atresia and the amount of blood behind it. If the patient is well past the age of puberty, and there is no fluid above the atresia, the probability is that the uterus is anomalous, so much so that menstruation could not come on even though the obstruction in the vagina were removed. So, before undertaking an operation for making a vaginal canal, rectoabdominal examination, under anesthesia if necessary, should be made to establish the size, shape, and probable development of the uterus. In cases of apparent absence of the uterus, rectovesical examination may be of assistance in locating a small nodule in the situation of the uterus.

The **treatment** depends on the circumstances of the case. If only a thin septum is present, it should be treated practically the same as an imperforate hymen—i.e., incised, to let out the blood, and then partially or wholly excised. If a considerable proportion or the whole of the vaginal canal is missing (Fig. 935), the treatment requires extended operative measures according to the special conditions present. It may be necessary to build up a whole new vagina. The details of this operative work are considered in the authors' *Operative Gynecology.* In Fig. 936 the results in a case of ours are shown; the Wharton type of operation was done. This patient has now been happily married for five years.

Mistakes of diagnosis can result in irreparable damage through injudicious operative procedures. In one of our cases a physician had mistakenly
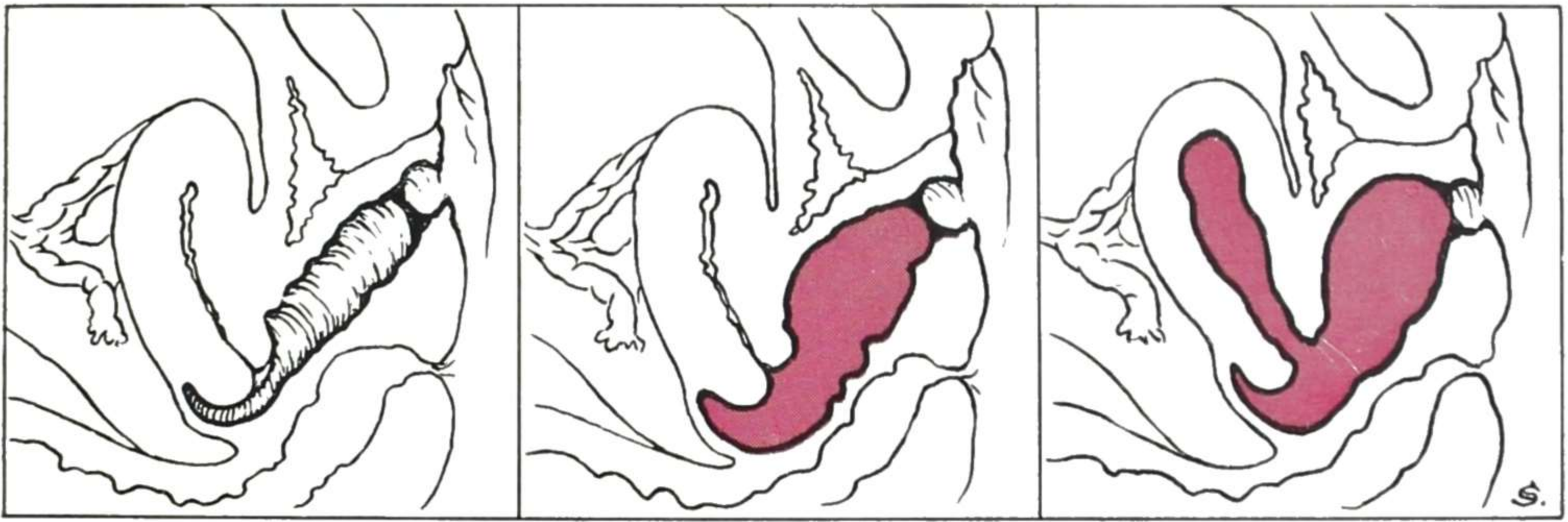
Fig. 928.   Fig. 929.   Fig. 930.

Fig. 928.—Indicating the location of the vaginal atresia in the case described in the text.

Figs. 929 and 930.—After puberty there began an accumulation of menstrual blood, which distended the vagina and later the uterus.
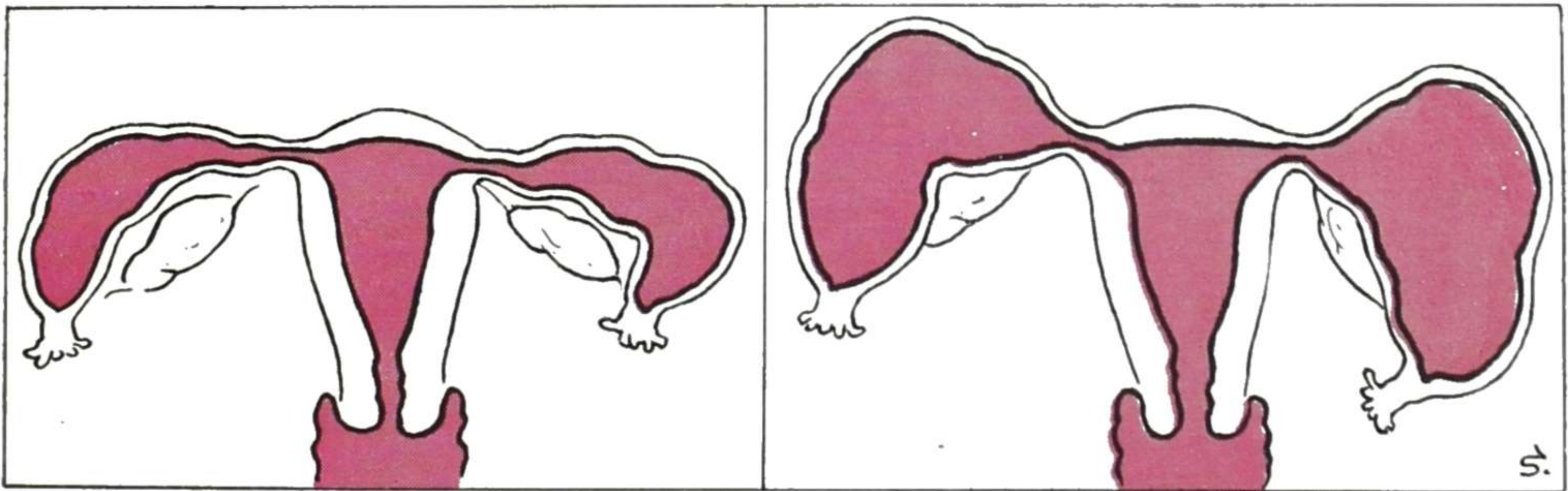

Fig. 931.   Fig. 932.

Figs. 931 and 932.—The retained blood extended into the tubes. Peritoneal irritation sealed the outer ends of the tubes, and the accumulating blood caused more and more distention.
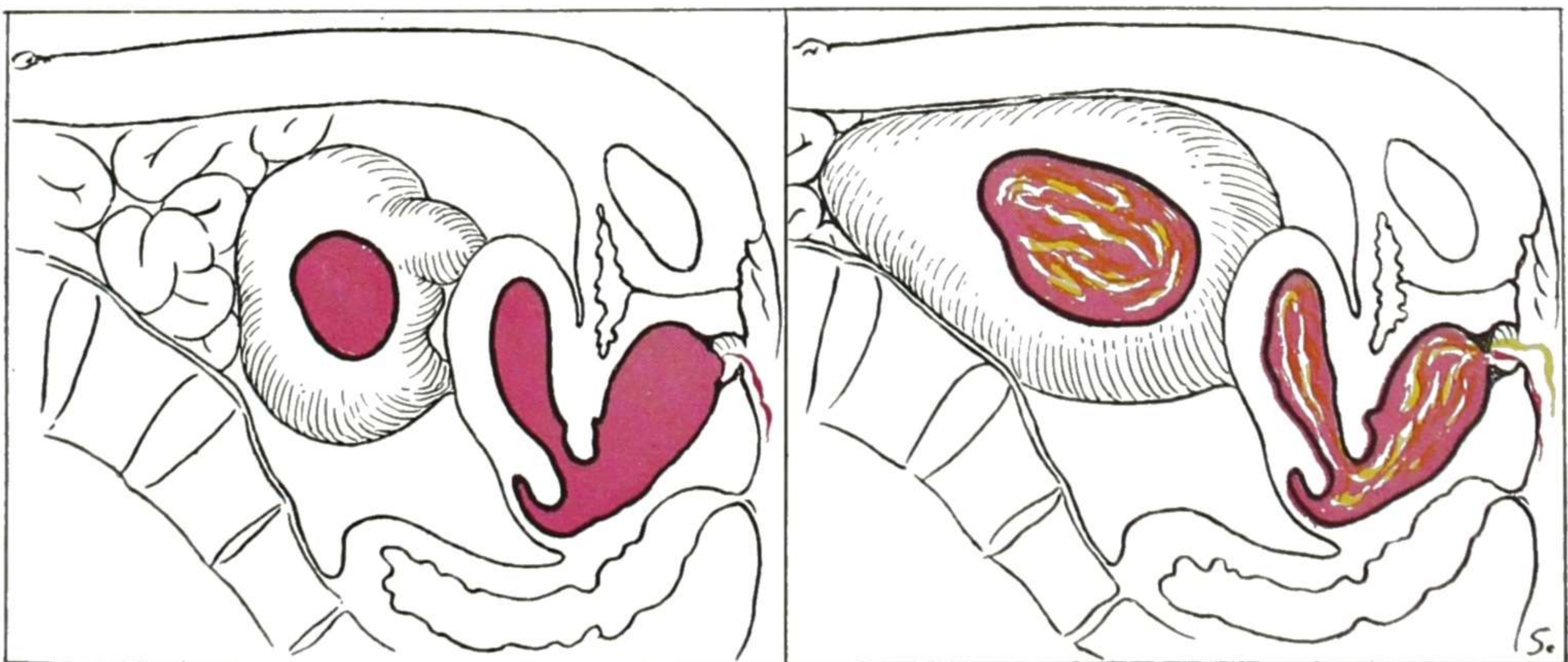

Fig. 933.   Fig. 934.

Fig. 933.—These blood-filled masses in the pelvis and lower abdomen had enlarged so gradually that they were not noticed, there being no acute symptoms leading to examination. Finally the vaginal distention thinned the abnormal septum to such an extent that a small opening occurred, and through this there was some leakage of the retained blood.

Fig 934.—Along this line of culture medium, inflammatory bacteria propagated into the vagina and then throughout the disintegrating blood mass. There was then rapid enlargement of the tubal masses, marked pain, high fever, sepsis, and the patient passed at once into a desperate condition—with the diagnosis obscure, until worked out as here shown.

thought that the urethra was the vagina and through a vaginal speculum in this urethra had cut into a bulging mass on the posterior wall of what he thought was the vagina. Following this procedure the patient passed blood on urination at each menstrual period. The pathology in this case consisted of an absence of the lower two-thirds of the vagina with a small pocket at the upper end into which the menstrual blood was collected. The incision made by the family doctor had connected this pocket with the bladder so that the child was menstruating through a fistula in the bladder.

Bryan, Nigro, and Counseller reported one hundred cases of congenital absence of vagina in which numerous surgical methods were used; the operative procedures are discussed in our *Operative Gynecology.*

Fig. 935.—Preoperative condition. Note normal clitoris and labia. Urethral meatus shows clearly and the space below it is area where incision is made. (From Crossen: J. Missouri M. A., December, 1947.)

Acquired Atresia.—In a considerable proportion of the cases, marked stenosis of the vagina, amounting almost to atresia, is acquired. Such a condition may result from injuries in childhood or inflammation, particularly the gonorrheal vaginitis of childhood and severe inflammations following the exanthemas. Congenital syphilis also may cause it, following severe ulceration. In later life, scar tissue resulting from injuries in labor is the most frequent cause of narrowings in the canal and bands and constrictions and distortions. Other causes in the adult are syphilitic ulceration, injuries, and severe destructive inflammations. A pessary left in the vagina for several years may lead to such a result. In rare cases even complete atresia may result from some one of these causes. The atrophic vaginitis or "adhesive vaginitis" of old age (senile vaginitis) leads to adhesion of the walls of the vagina and stenosis and partial obliteration of the canal. The treatment for acquired stenosis or atresia of the vagina is practically the same as for the congenital. The acquired form, however, is, when extensive, likely to be more difficult of satisfactory treatment on account of the large amount of scar tissue in the vicinity.

Double Vagina

This consists usually simply in a longitudinal septum dividing the vagina into two canals (septate vagina). The vagina with entirely separate walls is a much rarer condition. The longitudinal septum is the persisting fused wall of the two müllerian ducts, as already pointed out. It may extend the whole length of the vagina, giving two openings at the vestibule, and half the cervix in each upper end (Figs. 937 and 938). On the other hand, it may consist simply in a septum extending part way. Even when the septum extends the
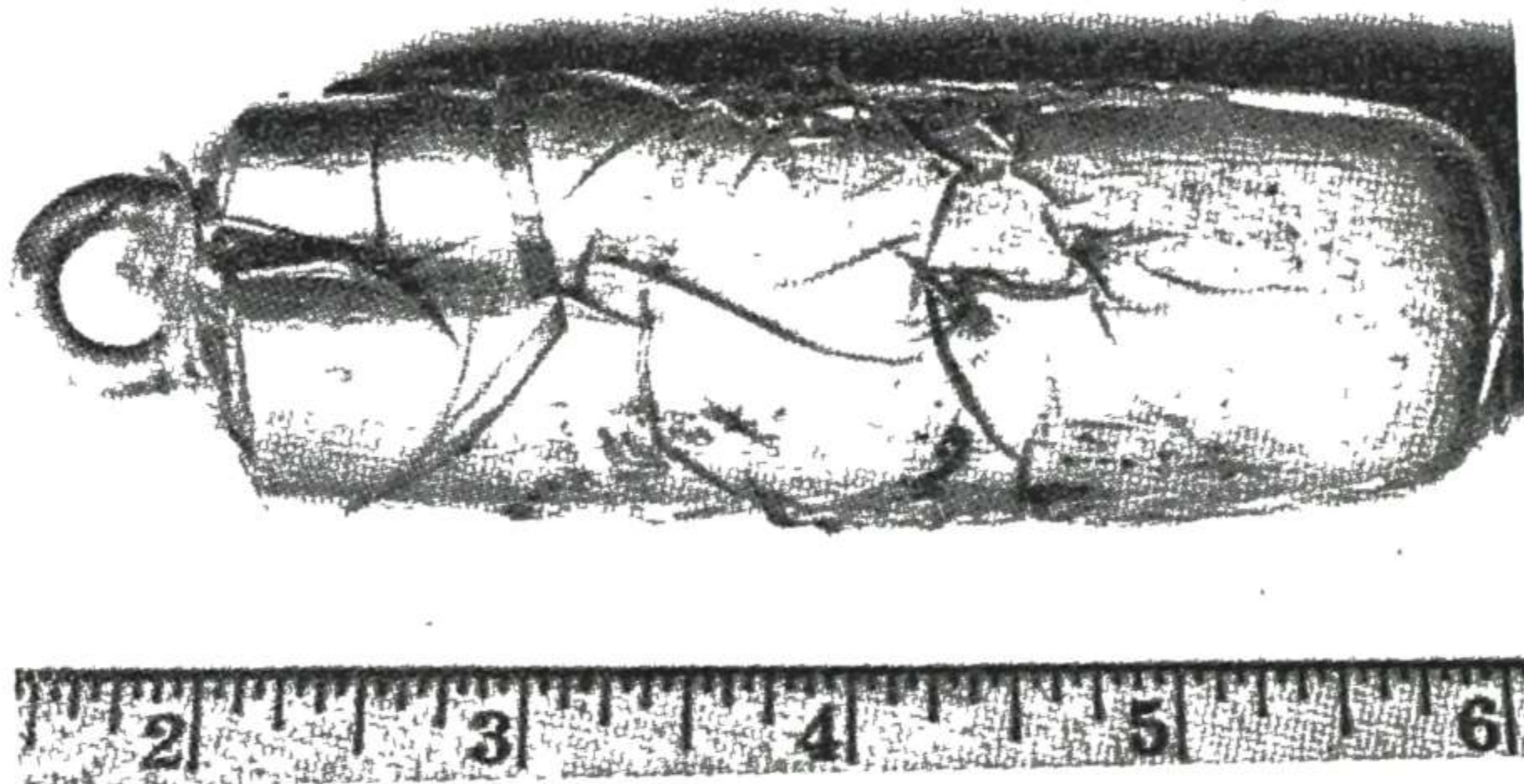
A.
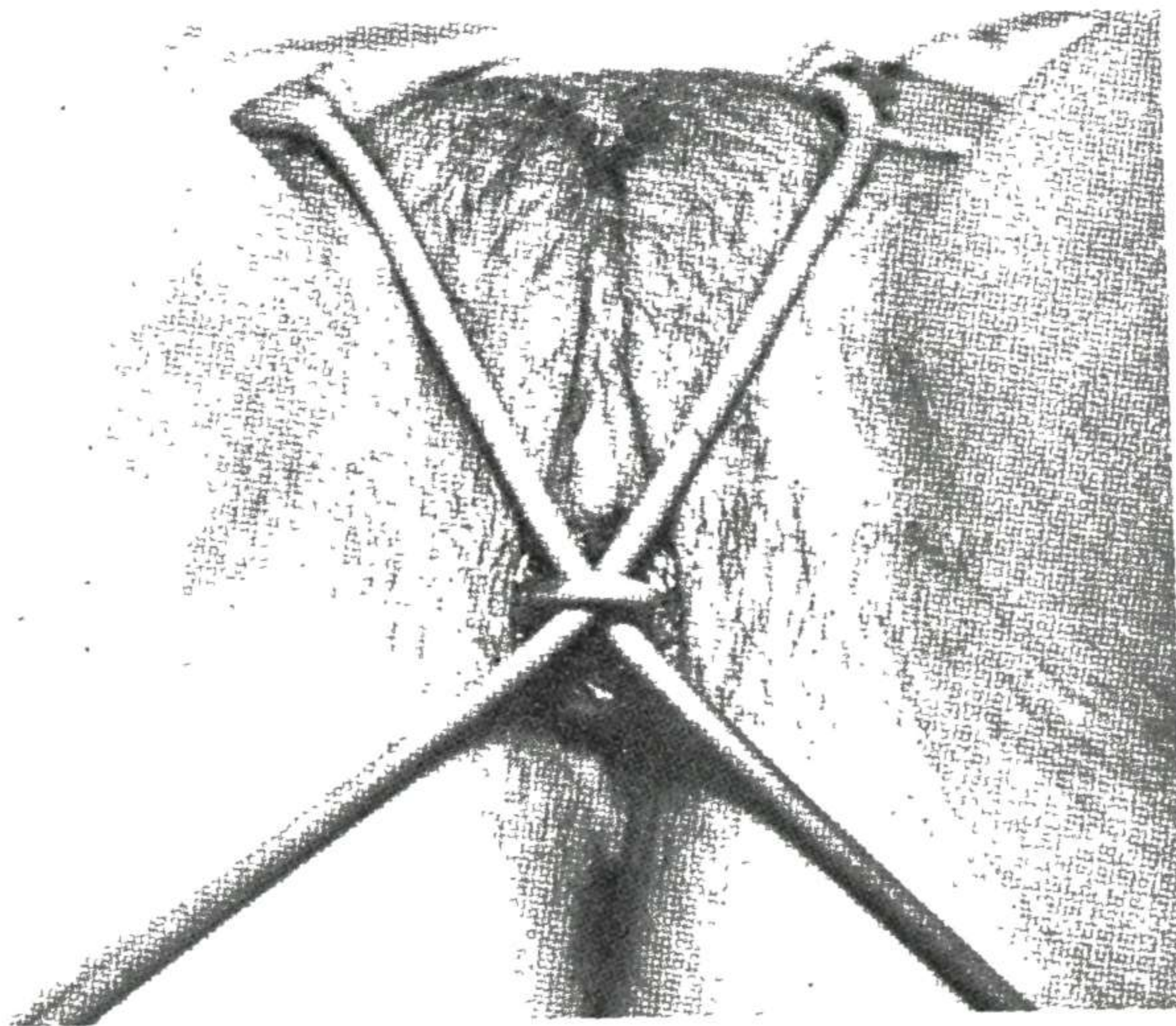
B.

Fig. 936.—*A,* Showing balsa wood plug with groove for urethra. Condom covering it is wrinkled. Screw eye at outer end through which rubber tubing passes.

B, Showing plug in place in vagina. Rubber tubing passes through screw eye and crosses to the opposite side. Rubber tubing fastens to belt in front and back. This holds the plug in place even with the patient up and around.

full length of the vagina, one canal is usually so much smaller than the other and placed so far to one side that it does not interfere with coitus or pregnancy. In fact the opening of one canal may be so flattened out at the side of an apparently normal vaginal opening that it is not noticeable except on very close inspection. In such a case, however, when the slit beside the vaginal opening is noticed, further examination may reveal a rudimentary canal of

considerable size, sometimes almost as large as the patulous one. At the upper part of each vagina is one-half of the cervix. When labor takes place in a case of double vaginal canal, the septum is likely to be torn, partially or completely, converting the two canals into one. Portions of the septum may remain as a partial septum at the upper part of the vagina or as irregular bands and tags.

The treatment of double vagina is simple. If the septum is causing any obstruction or disturbance, it is divided or, better still, largely excised, so that the two vaginal canals are converted into one.
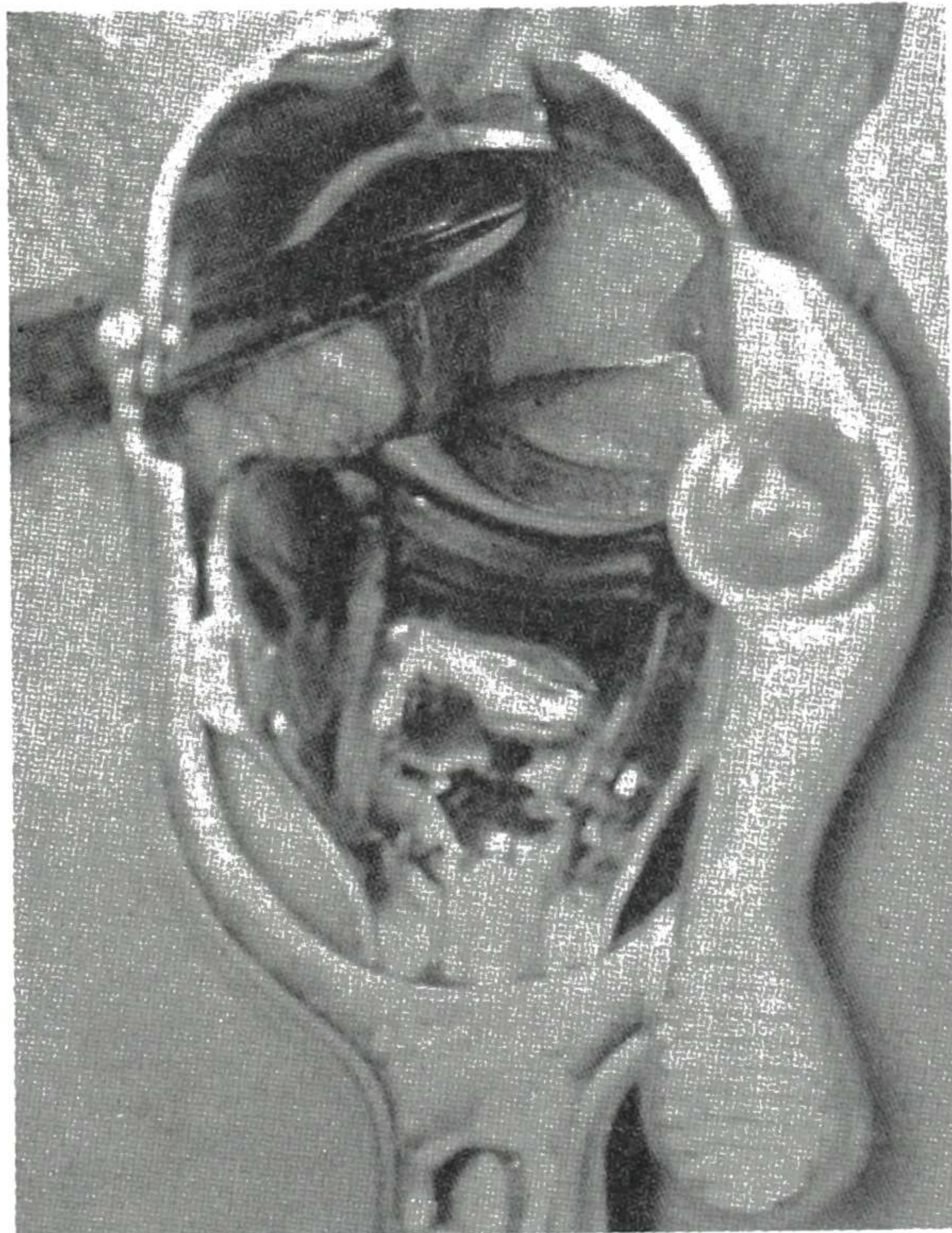
Fig. 936.—*C*, Vagina one month after operation. Speculum in full length. Glistening epithelium seen at upper end of vagina.

Vagina Opens Into Urethra

When examination reveals no vaginal opening at the vestibule, that does not nec_ssarily mean no vagina. There may be a fairly well-developed vagina opening into the urethra.

Barrows and Block reported such a case, in which the patient menstruated through the urethra. The condition is shown in Fig. 939, *A*. Operation consisted of opening the vagina into the vestibule and repairing the urethra, as shown in Fig. 939, *B*. In spite of dilatation treatments some stenosis persisted at the vaginal opening, and this was overcome by incisions, as indicated in Fig. 940, *A* and *B*.

Elden and also Jeffcoate reported somewhat similar cases. The latter designated the condition diphallus (Figs. 941 and 942). Young discussed this

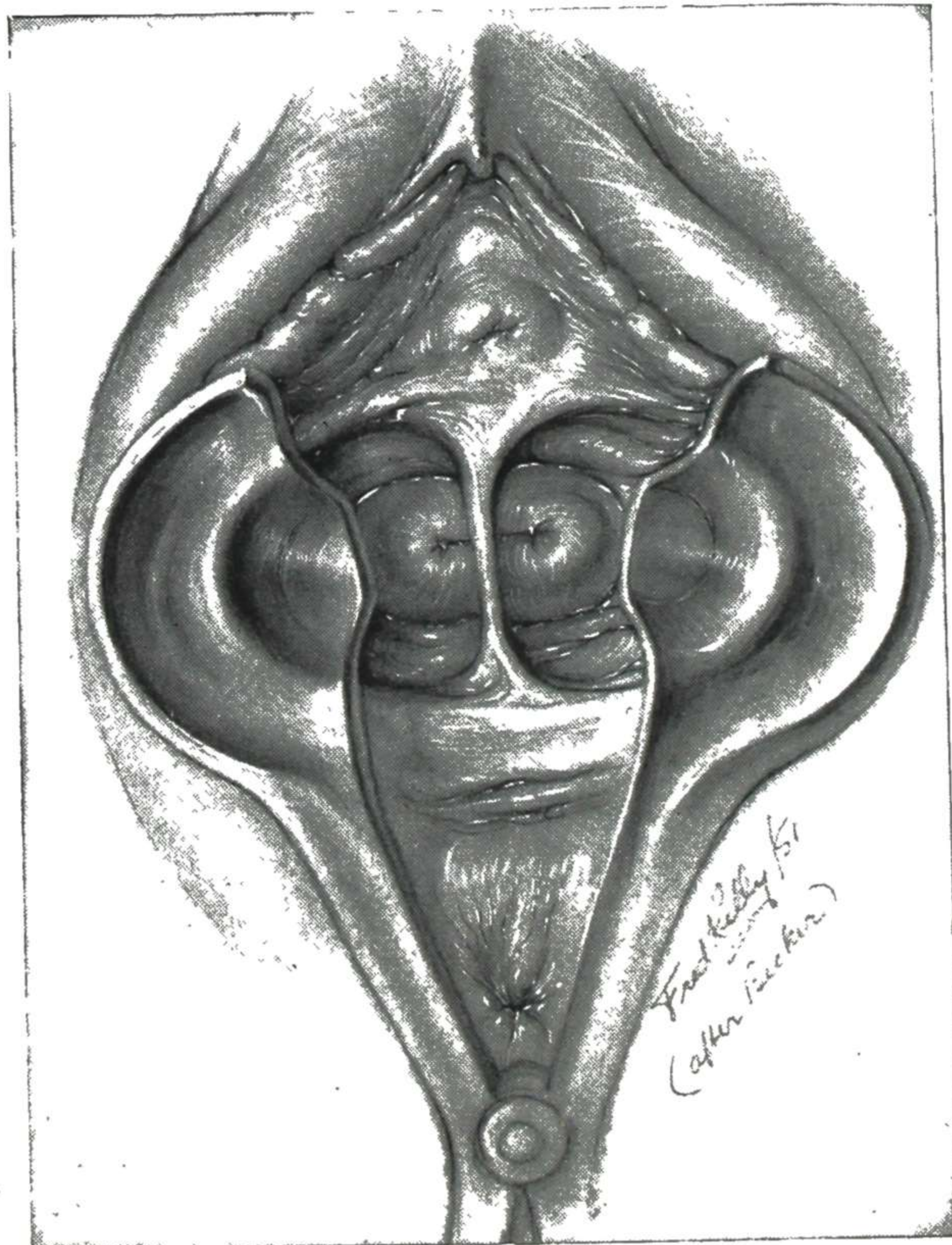Fig. 937.—Septum in vagina.   (From Jarcho: Am. J. Surg., January, 1946.)

Fig. 938.—The external genitals in a case of double vagina, with speculum introduced, exposing the two vaginal canals and the half cervix at the top of each.
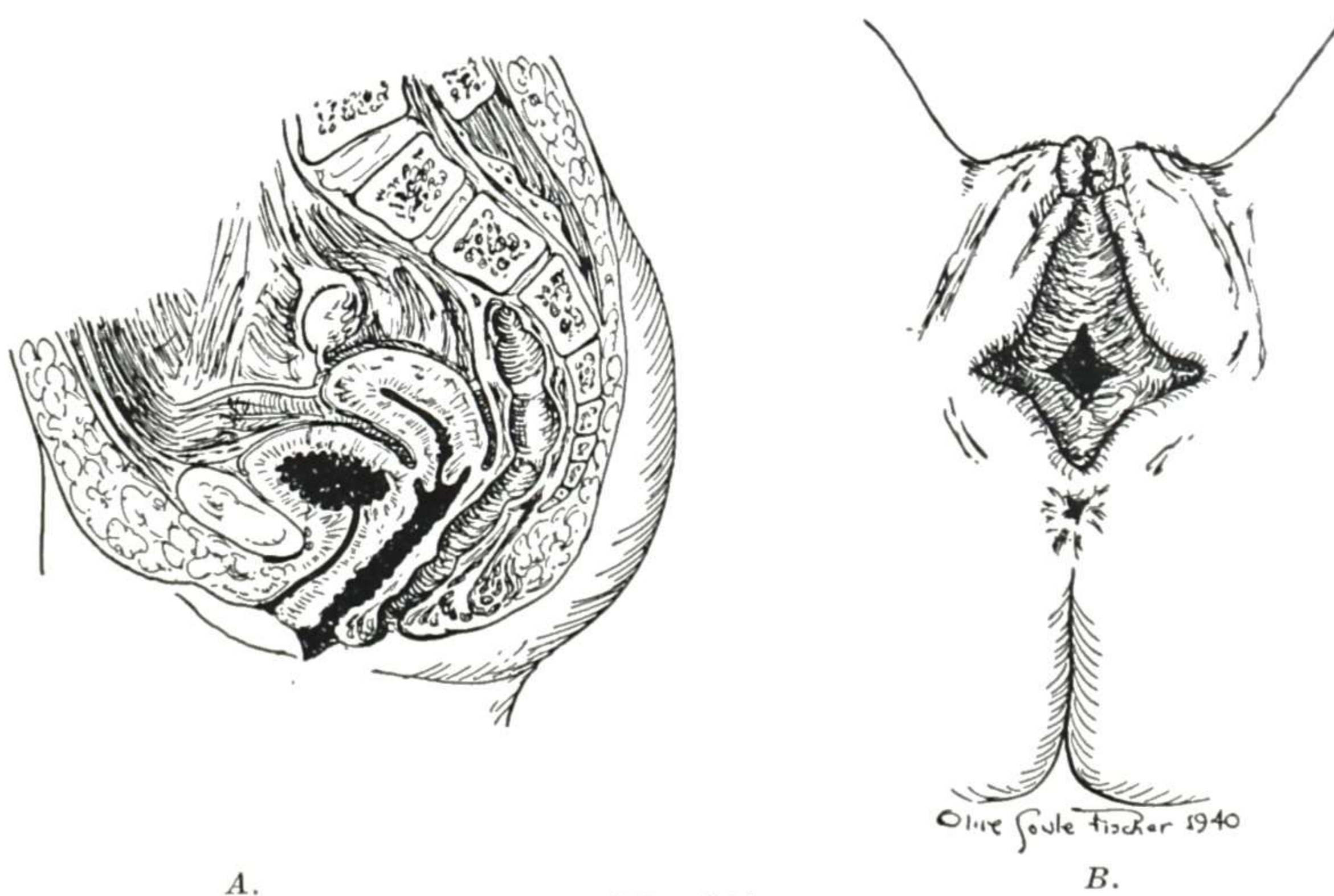
anomaly at length in his book on genital abnormalities, hermaphroditism and related adrenal diseases, and shows the cystoscopic appearance of the opening into the urethra, and also the cystoscopic appearance of the vaginal wall and cervix. The size of the anomalous vagina may be demonstrated by injection of opaque material.

A.

B.

Fig. 939.

A.

B.
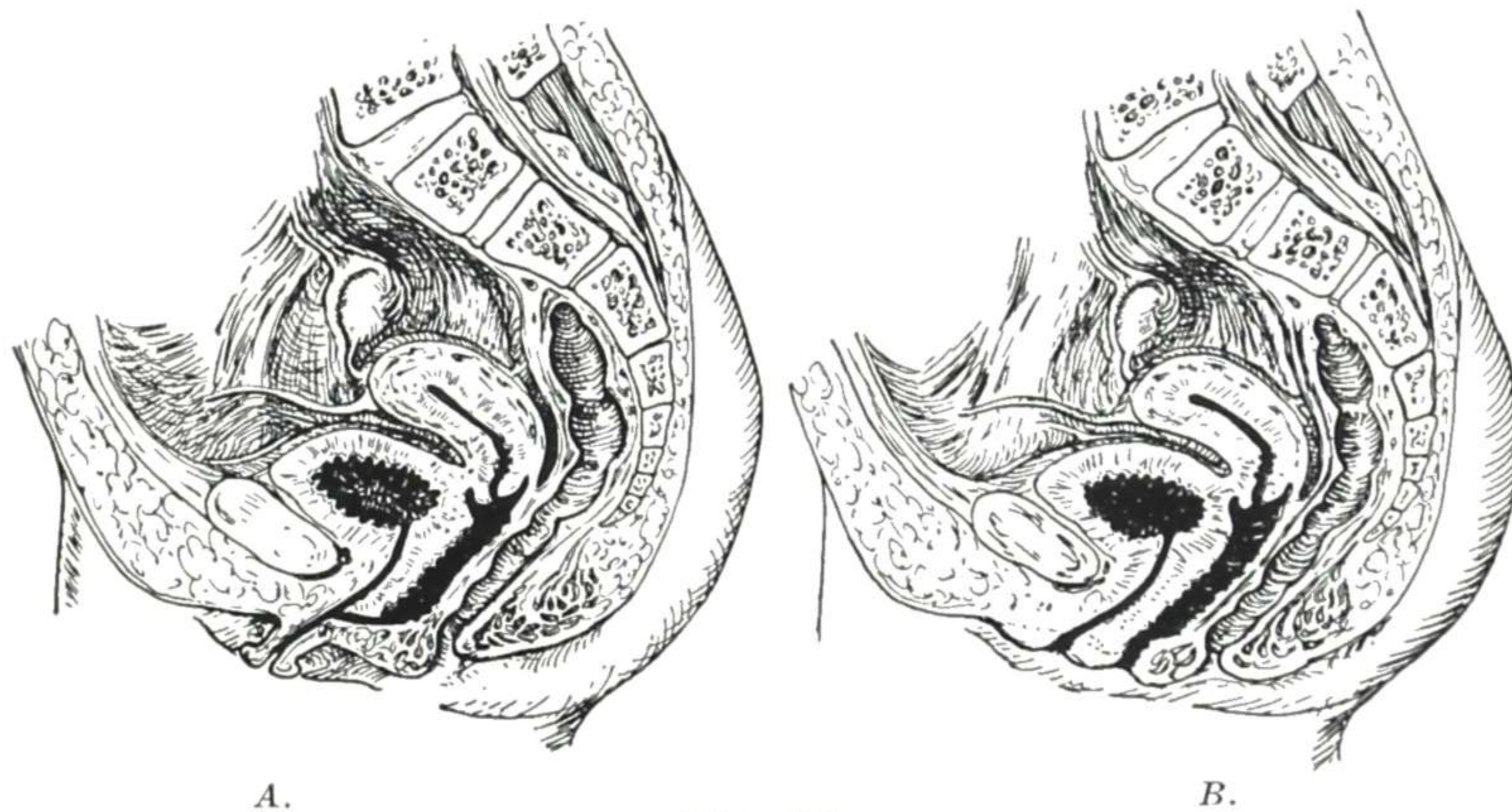
Fig. 940.

Fig. 939.—*A*, A malformation consisting of a vagina which opened into the urethra instead of into the vestibule. *B*, Result of operation for opening the vagina into the vestibule and closing the opening into the urethra. (From Barrows and Block: Am. J. Obst. & Gynec.)

Fig. 940. *A*, Result of further operation to enlarge the vestibular opening of the vagina. *B*, Front view, indicating the site of the enlarged opening and the appearance of the abnormal clitoris. (From Barrows and Block: Am. J. Obst. & Gynec.)

Malformations of the Uterus

The formation of the uterus by the union of two tubes may result in certain malformations. Cases of uterine malformation are illustrated in Fig. 943, taken from an article by Fenton and Singh on pregnancy and malformations of the genital tract. A proposed method of classification of uterine and vaginal anomalies suggested by Monie and Sigurdson is given in the accompanying table. The simplex is the normal condition of a single uterus, cervix, and vagina. Illustration of the various nomenclatures is shown in Fig. 944, and an illustration of their use is shown in Fig. 945.
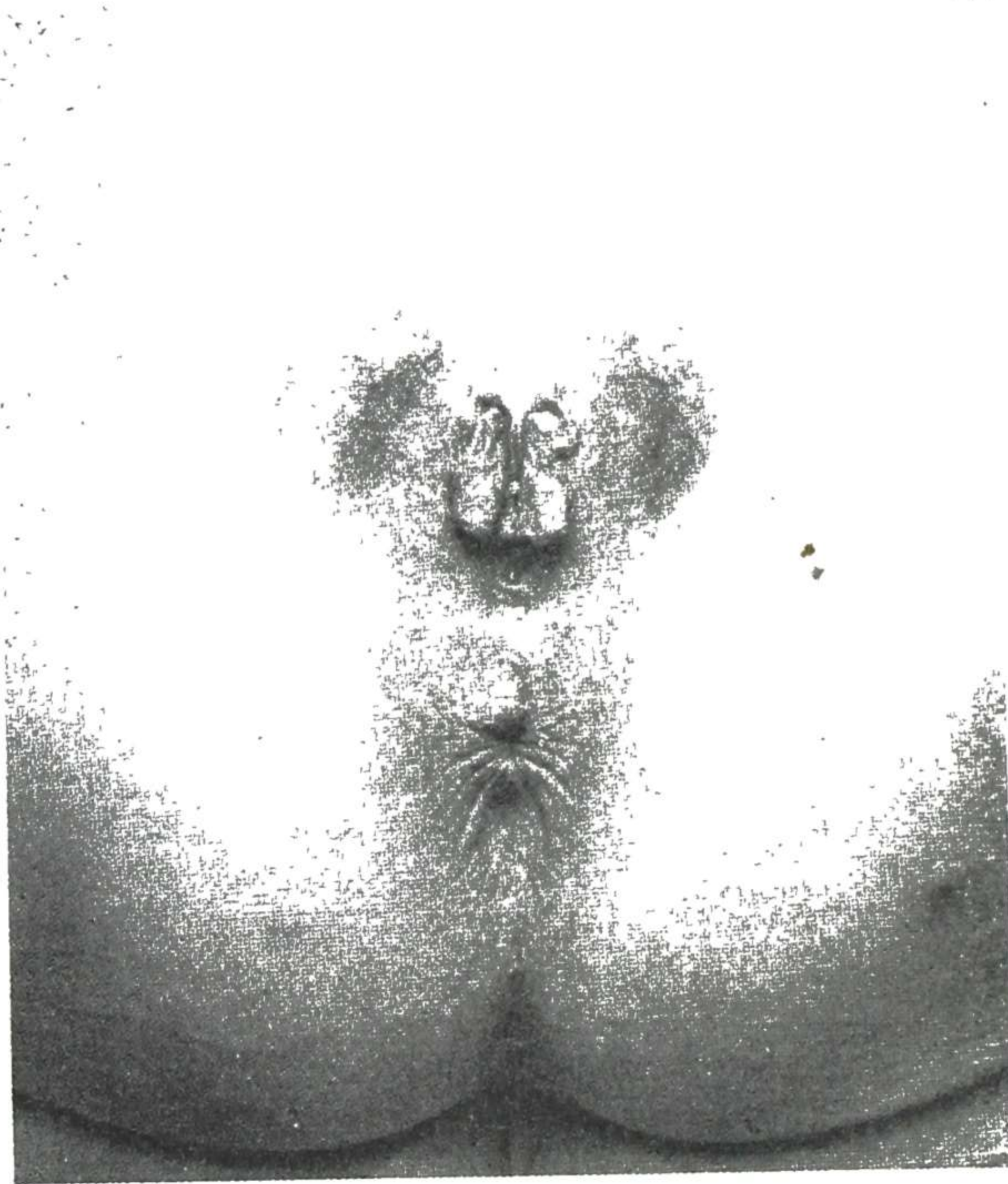
Fig. 941.—Photograph of Blair Bell's case (J. Obst. gynaec. Brit. Emp. 32: 112, 1925) showing bifid clitoris and epispadias. Note the depression in the mons, suggesting the presence of a split pelvis and absence of the hair over the central part of the pubes. (From Jeffcoate: J. Obst. & Gynaec. Brit. Emp. 59: 406, 1952.)
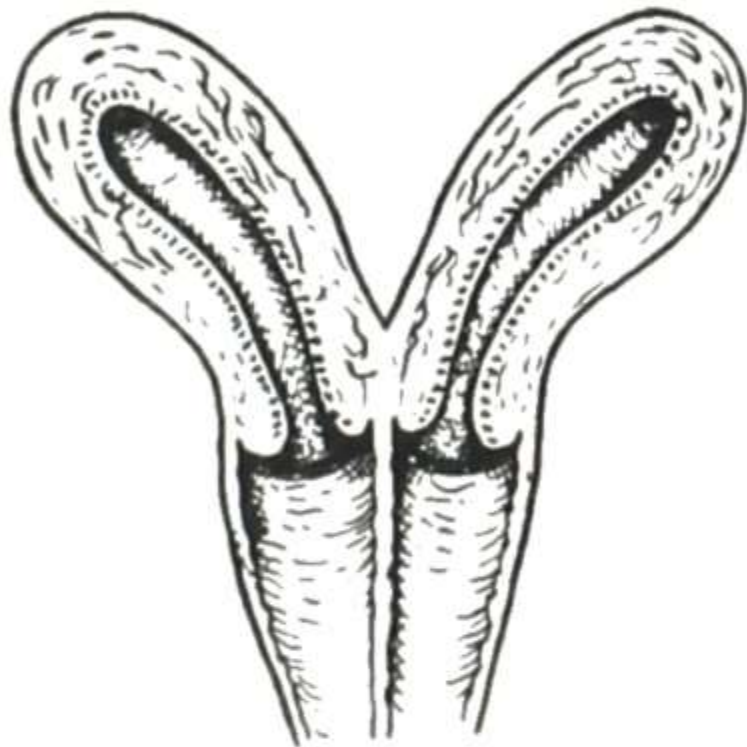

Fig. 942.—Vulva showing diphallus and arrangement of labia minora. The urethral orifice and lower vagina look normal. X-ray demonstrated absence of symphysis pubis. (From Jeffcoate: J. Obst. & Gynaec. Brit. Emp. 59: 406, 1952.)
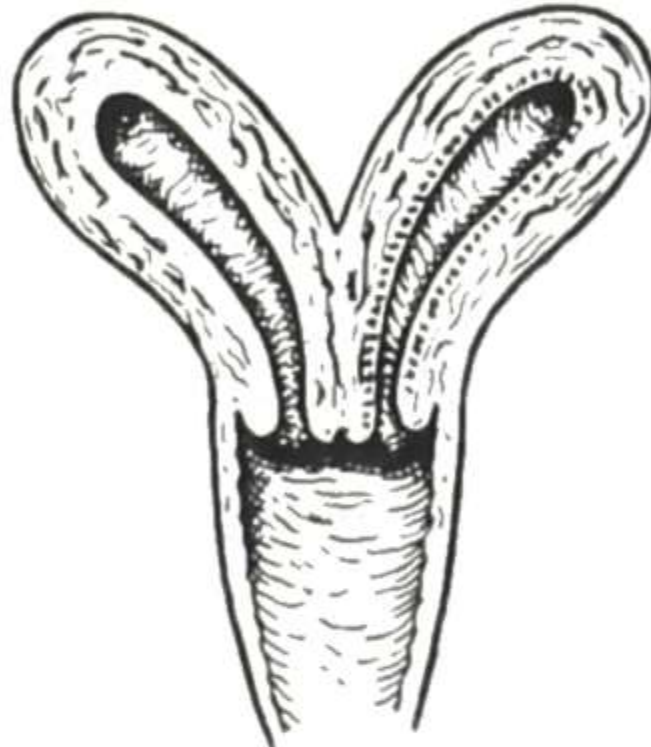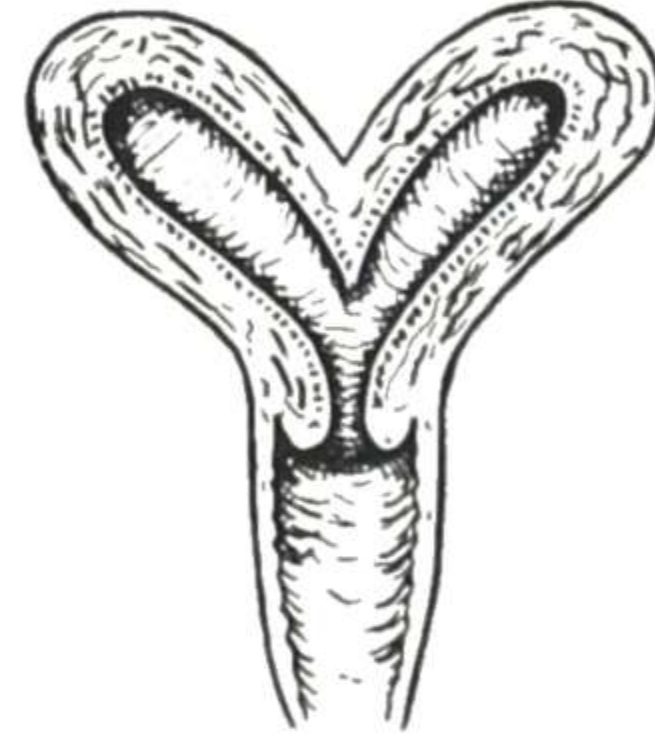
Uterus simplex

Uterus didelphys

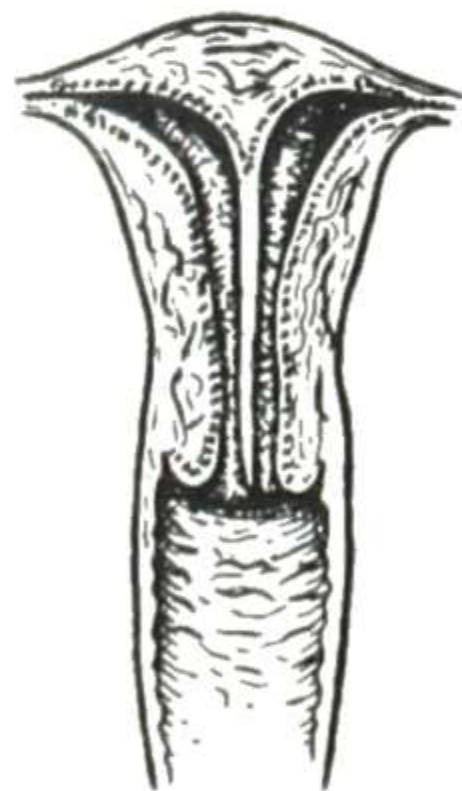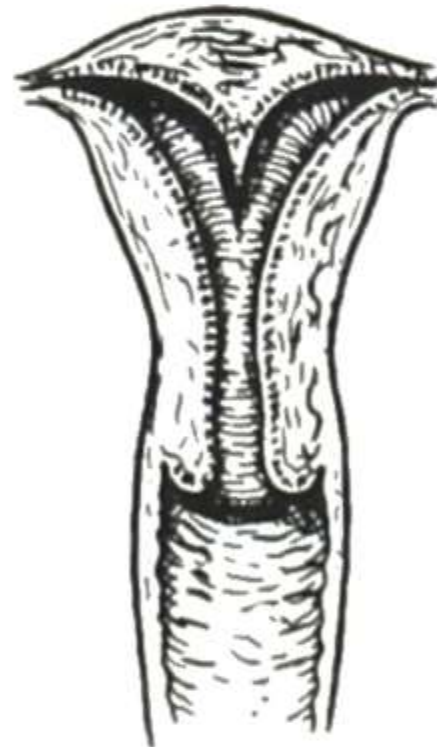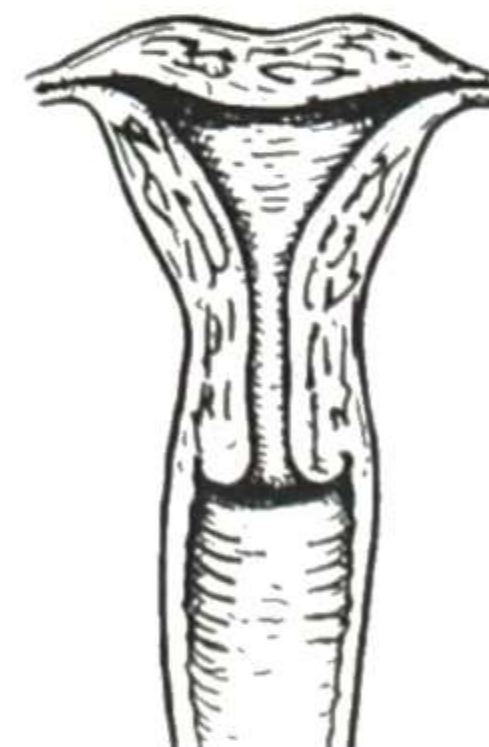Uterus duplex
bicornis bicollis
Vagina simplex

Uterus bicornis
unicollis
Vagina simplex

Uterus septus

Uterus subseptus

Uterus arcuatus

Uterus unicornis

Septate vagina

Congenital stricture
of the vagina

Fig. 943.—Congential abnormalities of the female reproductive tract. (Reproduced in part from Jarcho: Am. J. Surg., January, 1946.) (From Fenton and Singh: Am. J. Obst. & Gynec., April, 1952.)

SCHEME FOR CLASSIFICATION OF CONGENITAL ANOMALIES OF UTERUS AND VAGINA

Uterus	Corpus (Co)	Nullum	0		
		Simplex	I		
		Duplex	II		
		Arcuatum	Arc		
		Septum	Sep		
		Bicorne	Bi		
		Unicorne	Uni		
	Cervix (Ce)	Nulla	0		
		Simplex	I		
		Duplex	II		
Vagina (V)		Nulla	0		
		Simplex	I	Sagittale	Sag
		Duplex	II	Transversum	Trans
				Coronarium	Cor

Additional Qualifying Terms

Sinistra -trum, (sin): left
Dextra -trum, (dex): right
Immatura -um, (imm): rudimentary
Contracta -um, (contr): narrowed
Imperfecta -um, (imp): incomplete

Septate Uterus, Double Uterus.—The malformation may consist simply of a partial or complete septum in an otherwise normal uterus (uterus septate) or of a rudimentary horn with a nearly normal uterus or of a uterus with a body divided into two horns (uterus bicornis) or of a double uterus, with the body and cervix of one side separate from the body and cervix of the other side (uterus didelphys) or of a "unicorn uterus"—i.e., uterus made up of müllerian duct of one side only, the other being absent or nearly so. The most severe grades of deformity are very rare, though they are to be thought of in the diagnosis in puzzling cases. A septum in an otherwise normal uterus is discovered only by intrauterine manipulation, such as curettement or the introduction of the hand after labor for the removal of adherent placenta or for other reasons.

No treatment for double uterus is required ordinarily, with the exception of the precaution, when curetting the uterus, to be certain that both cavities are clear. It is appreciated, of course, that in this connection, and also in double uterus, pregnancy may take place in each of the two cavities, and at different times, producing various surprising results; such an unusual case is shown in Fig. 946, taken from Jarcho's article. Fenton and Singh review 146 pregnancies in malformations of the genital tract and give suggestions on the management of such cases. Diagnostic points are shown in Fig. 947.

Shelley reported a case of septate uterus, with adenocarcinoma in one side and a pedunculated polyp in the other, and remarked:

If the curette had gone into the right cavity instead of the left the uterine polyp would have been removed and might well have been considered to be the sole cause of the bleeding. Had this happened, the opportunity for early removal of the adenocarcinoma of the uterus might have been lost, unless there was considerable continued bleeding after discharge from the hospital. When the pieces of adenocarcinoma were obtained with the curette, no additional curetting was done. Had the polyp been removed first, of course, a thorough curettage would have followed. But it is possible to see how the curette might have gone into only one cavity of the uterus.

Corpus Simplex	Corpus Septum	Cervix Simplex	Cervix Duplex
(a) Co-I	(b) Co-Sep	(g) Ce-I	(h) Ce-II
Corpus Bicorne	**Corpus Duplex**	**Vagina Simplex**	**Vagina Duplex (Sagittale)**
(c) Co-Bi	(d) Co-II	(i) V-I	(j) V-II (sag)
Corpus Arcuatum	**Corpus Unicorne**	**Vagina Duplex (transversum)**	**Vagina Duplex (Coronarium)**
(e) Co-Arc	(f) Co-Uni	(k) V-II (trans)	(l) V-II (cor)

Fig. 944.—Outlines illustrating the principal terms used in table. The definitions of the terms are given below. (Note: "Corpus" is a neuter noun; "cervix" and "vagina" are feminine nouns.)

Nulla (*–um*); the structure is absent, e.g., "corpus nullum," no uterine body.

Simplex: single, as in normal state (*a, g,* and *i*).

Duplex: double (*d, h,* and *j*). In "corpus duplex" the uterine cavities do not communicate.

Arcuatum: while the fundus of the uterus is notched, the outline of the cavity is normal (*e*).

Septum: a septum extends from the fundus of the uterus to the cervix (*b*). Where only part of a septum is present, the qualifying word "imperfectum" (imp) can be used after septum, replacing the "subseptus" of other writers (Fig. 945, *c*).

Bicorne: two-horned. The two uterine chambers communicate inferiorly (*c*). Where one horn is rudimentary, the terms "immaturum" accompanied by "sinistrum" (sin), left, or "dextrum" (dex), right, may be used to qualify "bicorne," thus: Bi (sin. imm.) or Bi (dex. imm.) (Fig. 945, *e*).

Unicorne: where only one uterus of a "corpus duplex" is present (*f*). While the terms used to qualify "cervix" and "vagina" are self-explanatory, in the case of "vagina duplex" (V.II) it was felt that some indication should be given regarding the position of the vaginal septum which may lie in the sagittal, transverse, or coronal plane of the vaginal canal. Descriptive adjectives are thus given for these three planes, each being in the neuter case to qualify the understood word "septum."

(From Monie and Sigurdson: Am. J. Obst. & Gynec., March, 1950.)

Co-I; Ce-I; V-I	Co-II; Ce-II; V-II (sag)	Co-Sep (imp); Ce-I; V-I
(a)	(b)	(c)
Co-Arc; Ce-II; V-I	**Co-Bi (dex. imm.); Ce-I; V-I**	**Co-I; Ce-II; V-I**
(d)	(e)	(f)

Fig. 945.—Various cases as they would be classified according to the scheme in the accompanying table. (*a*) Uterus (corpus simplex et cervix simplex) et vagina simplex. (*b*) Uterus (corpus duplex et cervix duplex) et vagina duplex (sagittale). (*c*) Uterus (corpus septum imperfectum et cervix simplex) et vagina simplex. (*d*) Uterus (corpus arcuatum et cervix duplex) et vagina simplex. (*e*) Uterus corpus bicorne (dextrum immaturum) et cervix simplex et vagina simplex. (*f*) Uterus (corpus simplex et cervix duplex) et vagina simplex. (From Monie and Sigurdson: Am. J. Obst. & Gynec., March, 1950.)

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Fig. 946.—Coronal section showing both uteri in same case as Fig. 937. (From Jarcho: Am. J. Surg., January, 1946.)
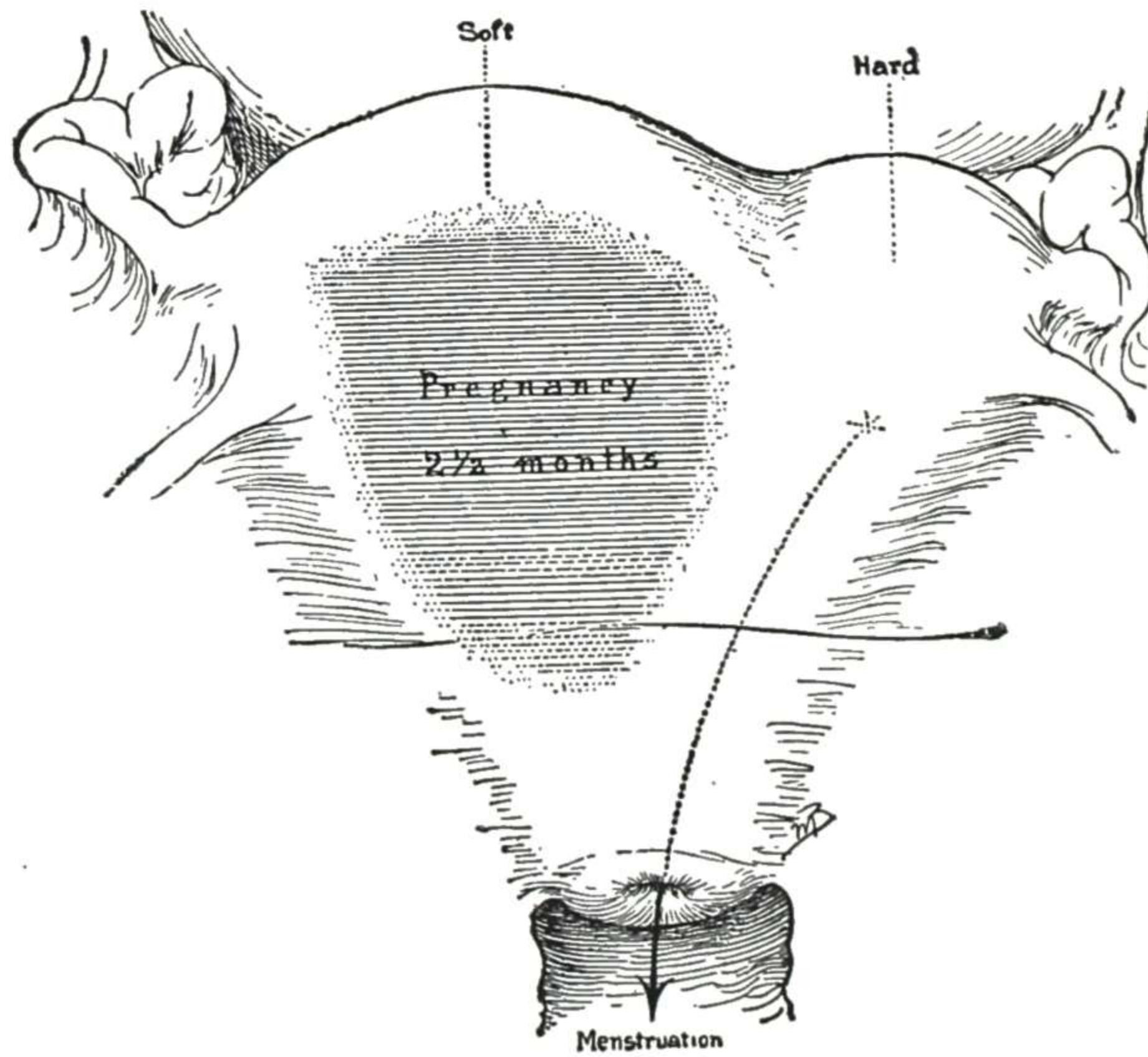
Fig. 947.—Pregnancy in the right half of a septate uterus. (From Kelly: Operative Gynecology.)

If the septum in a uterus gives trouble, it may be removed. Luikart reported such a case, the septum being associated with a bicornate condition of the uterus. Fig. 948 shows the outline of the cavity after removal of the septum. This method of outlining by opaque injection and x-ray may be employed for diagnosis in uncertain cases.

There may be also atresia at the lower part of a uterus, or of part of a malformed uterus, with a collection of menstrual blood in the cavity (hematometra), as shown in Figs. 949 and 950.

Fig. 948.—Lipiodol x-ray of bicornate uterus six weeks after removal of septum. (From Luikart: Am. J. Obst. & Gynec.)

Fig. 949.   Fig. 950.

Fig. 949.—Uterus distended with menstrual blood (hematometra) due to atresia of the cervix.

Fig. 950.—Double uterus with atresia in one side.
(From Montgomery: Practical Gynecology.)

Rudimentary Horn.—The uterine malformation of most practical interest is that of a rudimentary horn with an otherwise nearly normal uterus. This is not so very infrequent and many are the diagnostic difficulties that result

therefrom. Such a rudimentary horn extends outward from the main body of the uterus, and receives at its outer extremity the attachment of the fallopian tube and round ligament of that side. The point of attachment of the round ligament is, in some cases, the only decisive gross evidence as to whether the mass in question is an enlarged fallopian tube or a rudimentary horn of the uterus. The cavity of the rudimentary horn may be complete, extending

Fig. 951.—Uterus bicornis unilatere rudimentarius. "Of great clinical importance, because pregnancy may occur in the rudimentary horn, and such an accident is worse than ectopic gestation, with which it is usually confounded." (Drawing modified from DeLee to show a pregnancy in the rudimentary horn.) (From de Nicola and Petersen: Am. J. Surg., March, 1947.)
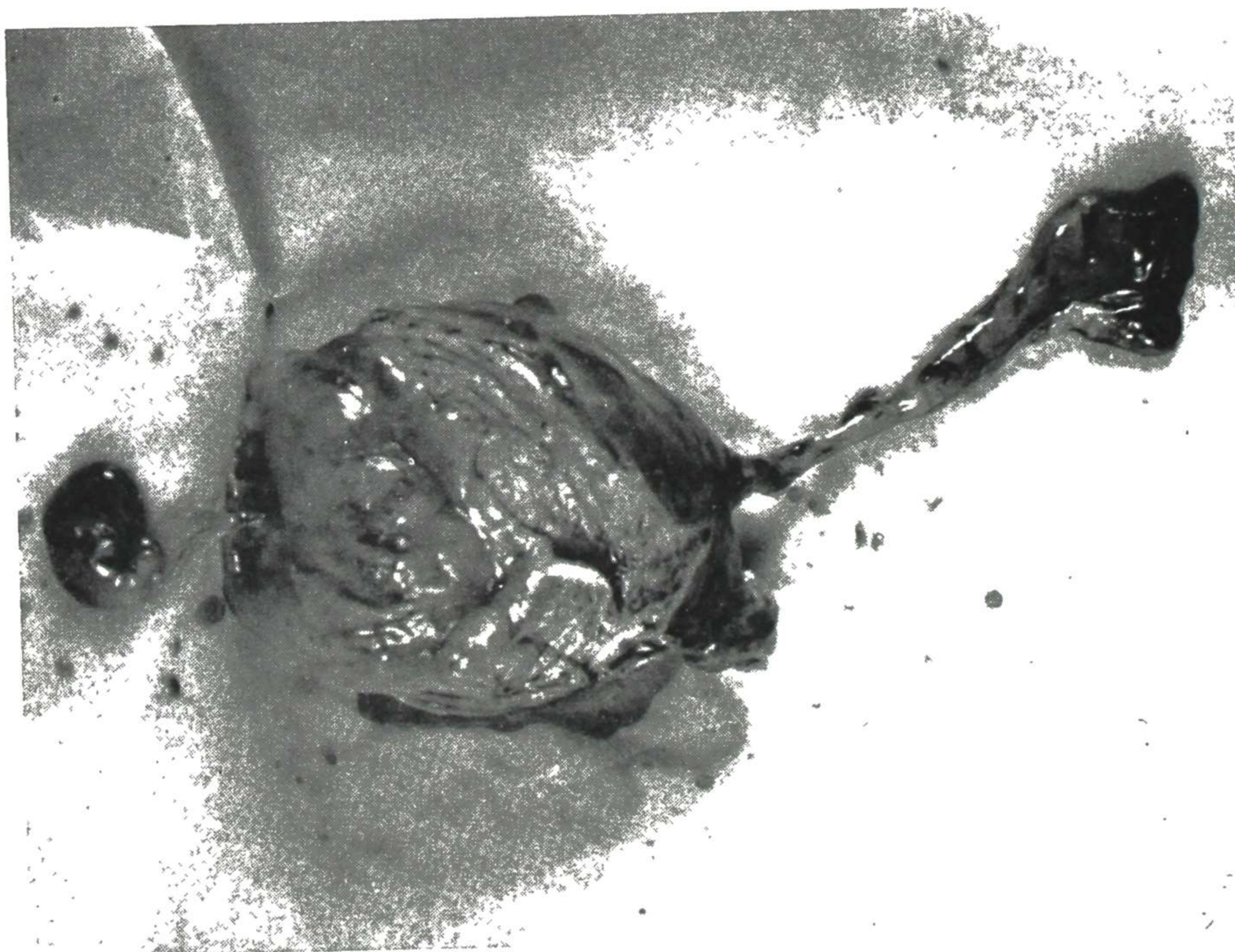
Fig. 952.—Specimen removed at operation showing fetus (at right edge of photograph), placental membranes, rudimentary horn, oviduct, and stump of left round ligament (actual size). (From de Nicola and Petersen: Am. J. Surg., March, 1947.)

all the way from the fallopian tube to the main cavity of the uterus, or it may be only partial, being absent at some part, or the cavity may be entirely absent, the horn existing merely as a musculofibrous cord connecting the fallopian tube and round ligament with the uterus. Most of the trouble resulting from a rudimentary horn comes from infection in it or pregnancy in it. Figs. 951 and 952 are from a case described by de Nicola and Petersen.

Fig. 953.—Skiagram taken on March 10, 1950, when the patient was 38 weeks pregnant, showing the attitude of hyperextension in the transverse lie—the "flying fetus." (From Denny: J. Obst. & Gynaec., Brit. Emp. June, 1951.)

The **symptoms** and **differential diagnosis** and **treatment** are the same as for similar affections of the fallopian tube, with the following special points:

1. The mass is usually connected to the uterus by a much broader attachment.

2. There is more enlargement of the uterus and distortion of its cavity.

3. The mass may become much larger without rupture if pregnant or without adhesions if inflammatory.

4. There may be a communication with the main uterine cavity. In most cases the condition is not thought of until found during the course of an operation for what was supposed to be some one of the more common affections. Even when thought of, a diagnosis is rarely possible (except in an examination under anesthesia), for it produces the symptoms and signs of more common
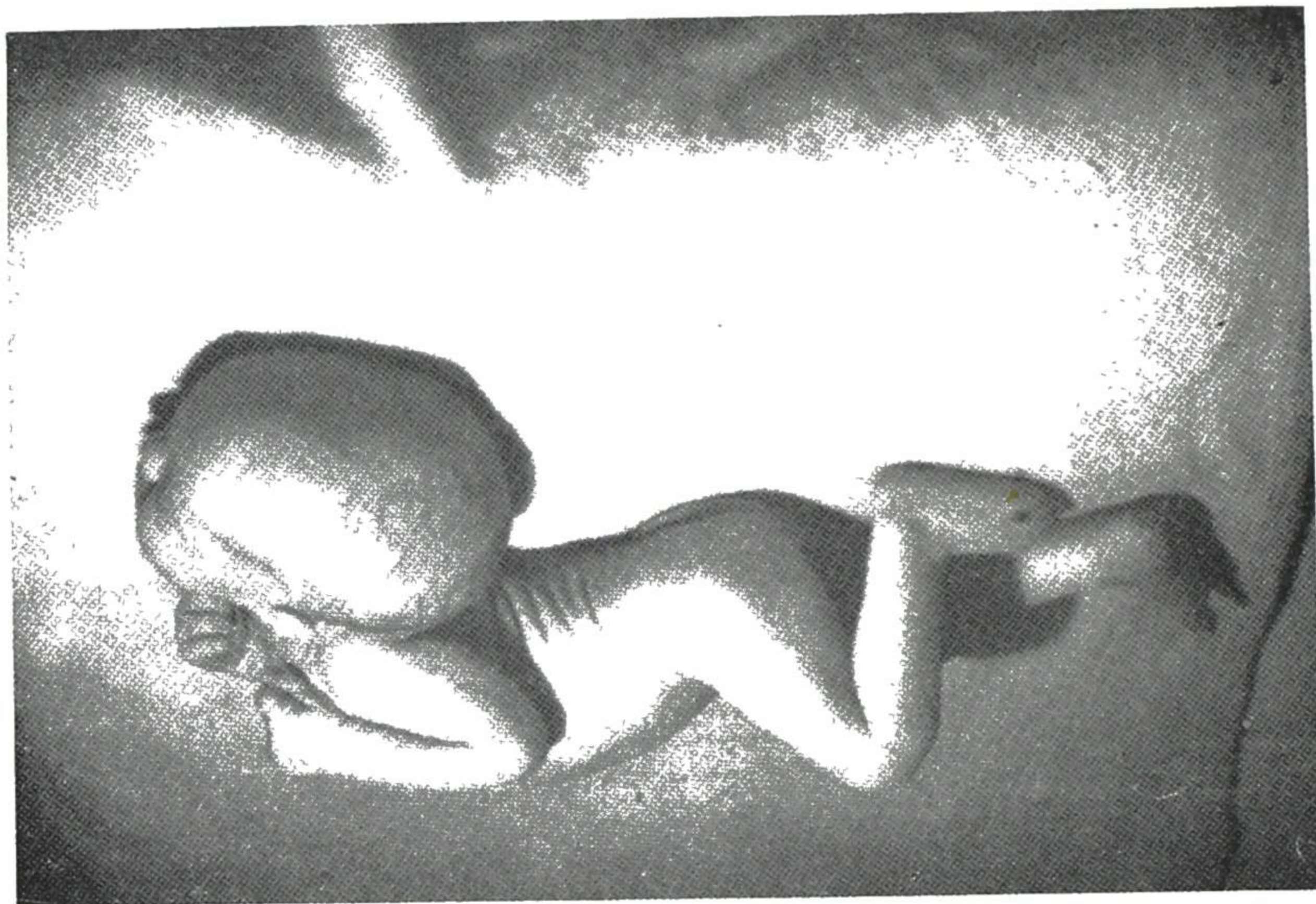
Fig. 954.—Hyperextension soon after delivery by caesarean section. (Mr. W. N. Searle's case. The pictures are reproduced by kind permission of Mr. G. F. Gibberd.) (From Denny: J. Obst. & Gynec., Brit. Emp., June, 1951.)
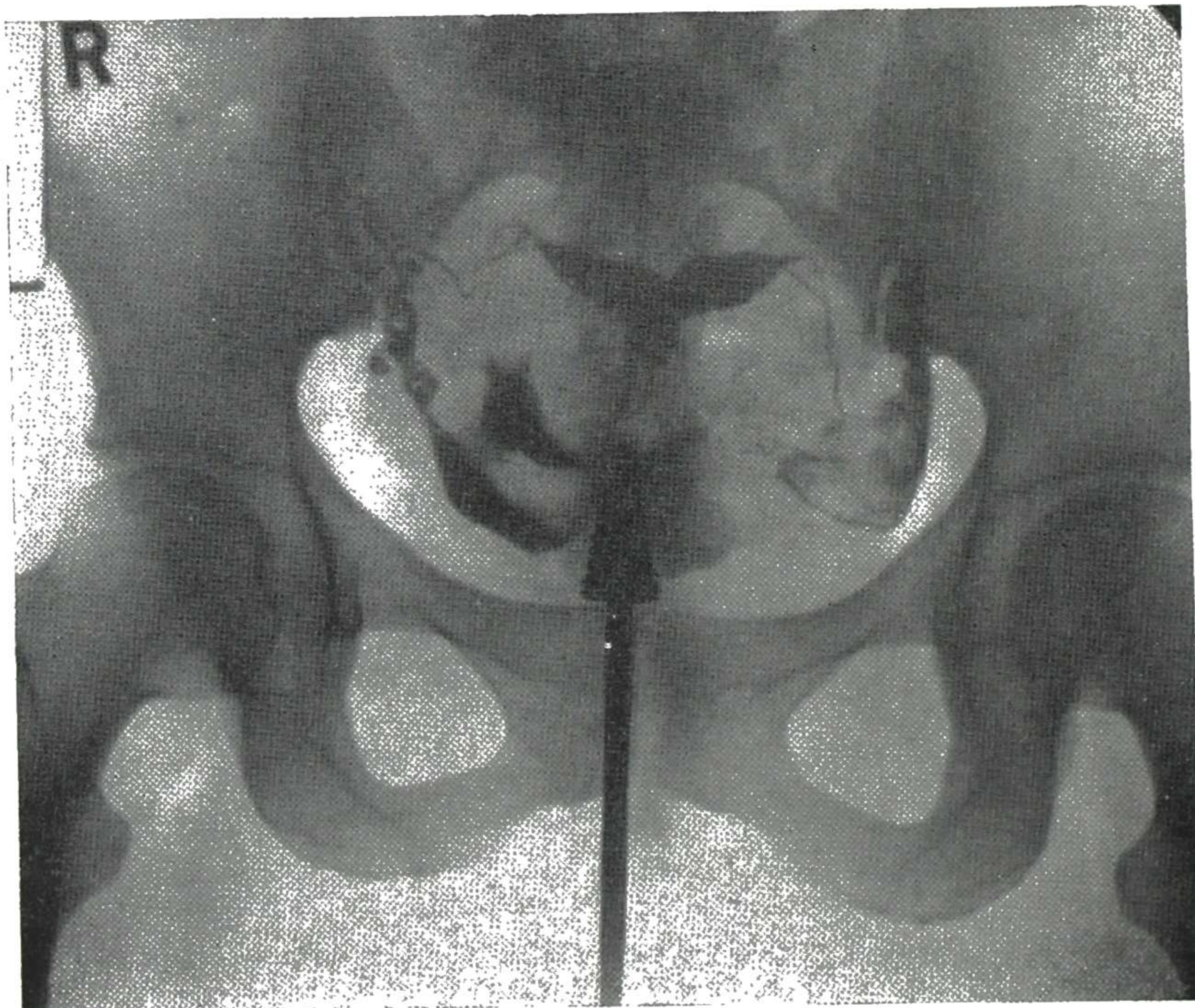
Fig. 955.—Hysterosalpingogram showing the features of the bicornate uterus in case shown in Figs. 953 and 954. This was carried out seven months after delivery. (From Denny: J. Obst. & Gynaec., Brit. Emp., June, 1951.)

conditions, and the trouble is naturally supposed to be some one of these more common affections. In some cases, however, there are anomalous symptoms or signs that make diagnosis difficult and doubtful, and arouse suspicion of this malformation. Sometimes there is decided resemblance to a fibroid. H. S. Crossen had one such case. The symptoms and signs were anomalous and puzzling. He made a diagnosis of probable fibroid with complications. Operation revealed a rudimentary uterine horn, with the remains of an early pregnancy in it. There was no fibroid.

5. An abnormal position of the fetus, either a transverse lie or the so-called "flying fetus," should make one suspicious of a congenital abnormality of the uterus. A recent case was reported by Denny (Figs. 953 to 955).

GROUP		GENITAL DEFECT	KIDNEY DEFECT	SPINA BIFIDA	CASE #	REPRESENTATIVE TYPE
Unilateral Complete Agenesis.	I	Right Left	Right Absent Left Absent	None None	(1) (2)	
Unilateral Partial Agenesis.	IIa	Right Left Left	Right Absent Left Absent Left (Pelvic)	None Sacral Lumbar	(3) (4) (5)	
Unilateral Partial Agenesis c̄ external communication.	IIb	Right Left	Right Absent Left Absent	None ?	(6) (7)	
Unilateral Partial Agenesis s̄ or s̄ external communication.	IIc	Right Right Left Left	Right Absent Right Absent Left Absent Left Absent	None Sacral None Sacral	(8) (9) (10) (11)	
Failure of Fusion Complete or Partial.	III	---- ---- ----? ----	None None Left Absent None	None Sacral None ?	(12) (13) (14) (15)	
Complete Agenesis.	IV	Complete Absence	Complete Absence	?	(16)	

Fig. 956.—Table of genitourinary defects associated with genital defects in development, seen on the Gynecologic Service of Washington University Medical School. These are to be reported by Ralph Woolf and Willard Allen in the near future, together with additional cases, making a total of 34 cases in all.

Malformations of the genitourinary tract associated with abnormalities of the genital tract have in recent years been extensively investigated. In all cases of genital malformation it is important that intravenous pyelograms be obtained. Experimental work on the causation of malformations has been mentioned above. Fig. 925 shows the similarity of the experimentally produced lesion to that found clinically. The chart shown in Fig. 956, compiled by Drs. Ralph Woolf and Willard Allen, illustrates the various urinary anomalies associated with 34 cases of genital malformations seen on the services of the Barnes and Maternity Hospitals. Eisaman and also Taylor state

that 90 per cent of patients having urinary abnormalities have associated genital malformation, but that only 30 to 40 per cent of those having genital malformations have an associated urinary abnormality. The kidney is usually either absent or abnormal on the side of the missing genital part. Fig. 957 shows a diagrammatic representation of a uterine and renal anomaly in a case reported by Schattenberg and Ziskind, and Fig. 958 shows the x-ray findings in a case of Seymour Monat of our department.
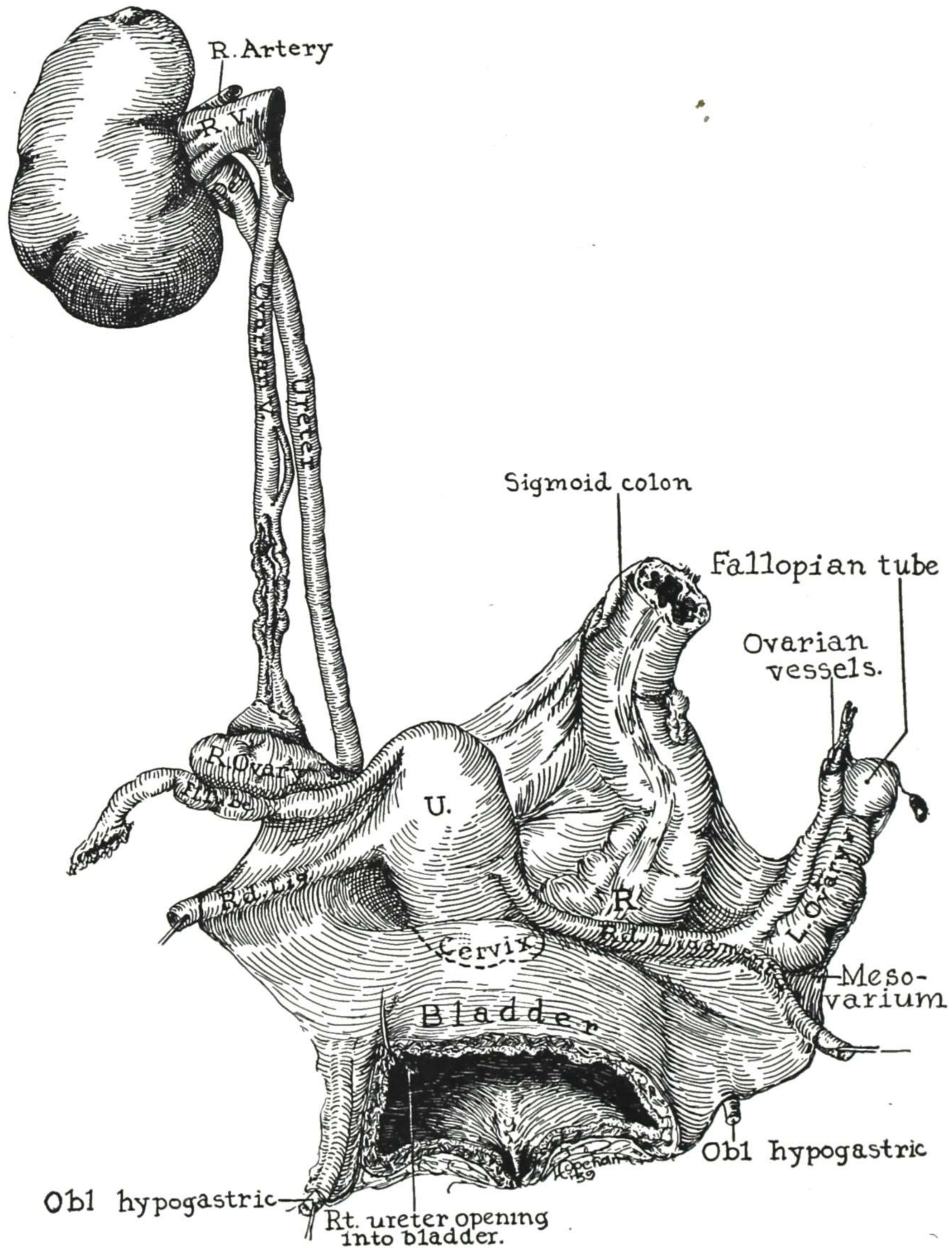
Fig. 957.—Diagrammatic representation of the uterine and renal anomaly and its relationships. (From Schattenberg and Ziskind: Am. J. Obst. & Gynec., August, 1940.)

Pseudohermaphroditism

A true **hermaphrodite** is, according to Ahlfeld's definition, "an individual with functionating active glands of both sexes, provided with excretory ducts." No such case has been reported in which the diagnosis has been fully accepted,
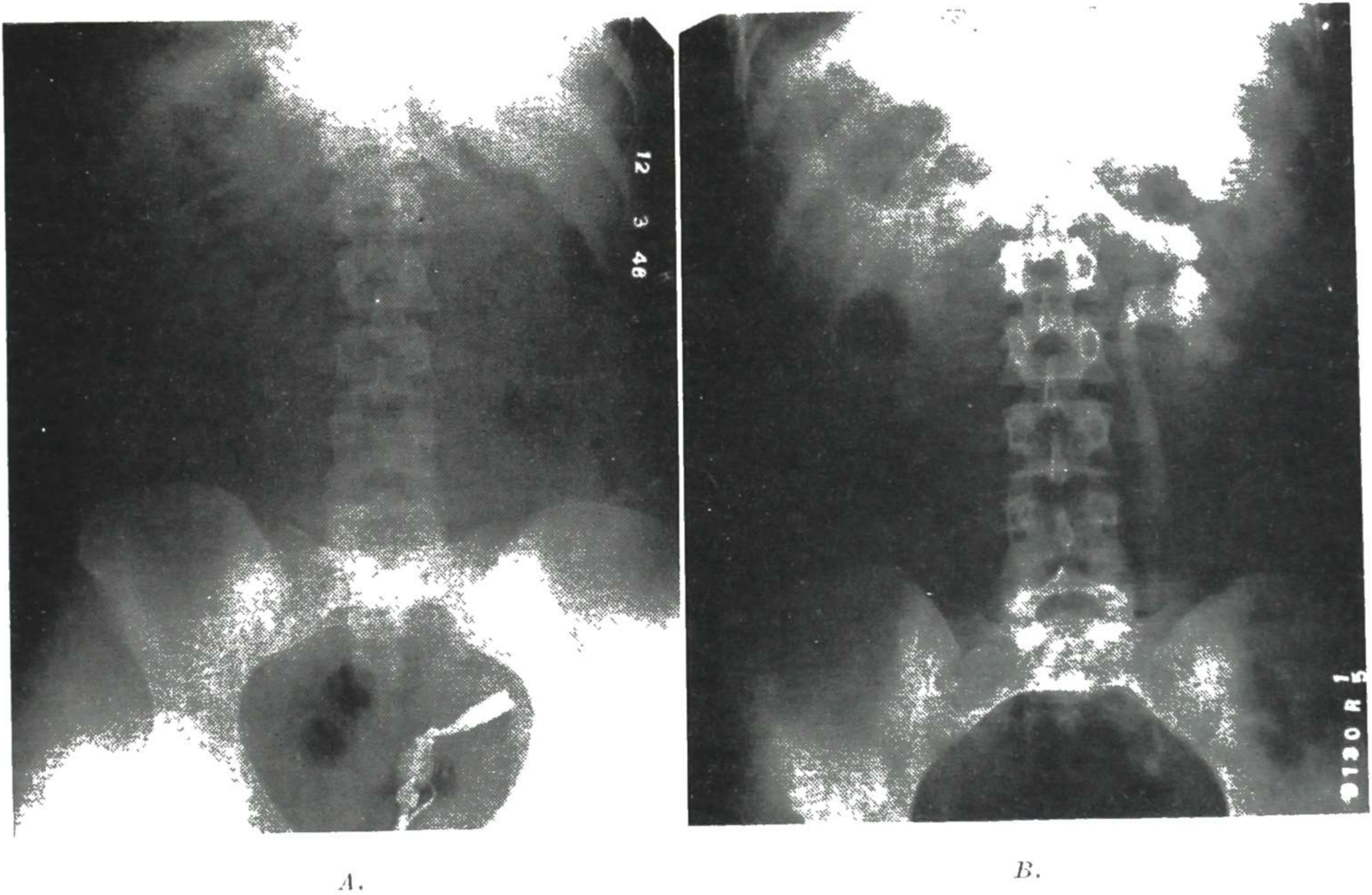
A.   B.

Fig. 958.—*A*, Hysterosalpingogram showing uterus unicornis.   *B*, Intravenous pyelogram of same case showing good kidney and ureter on the same side and an absence of the opposite ureter and kidney.   (Case presented through the courtesy of Dr. Seymour Monat.)
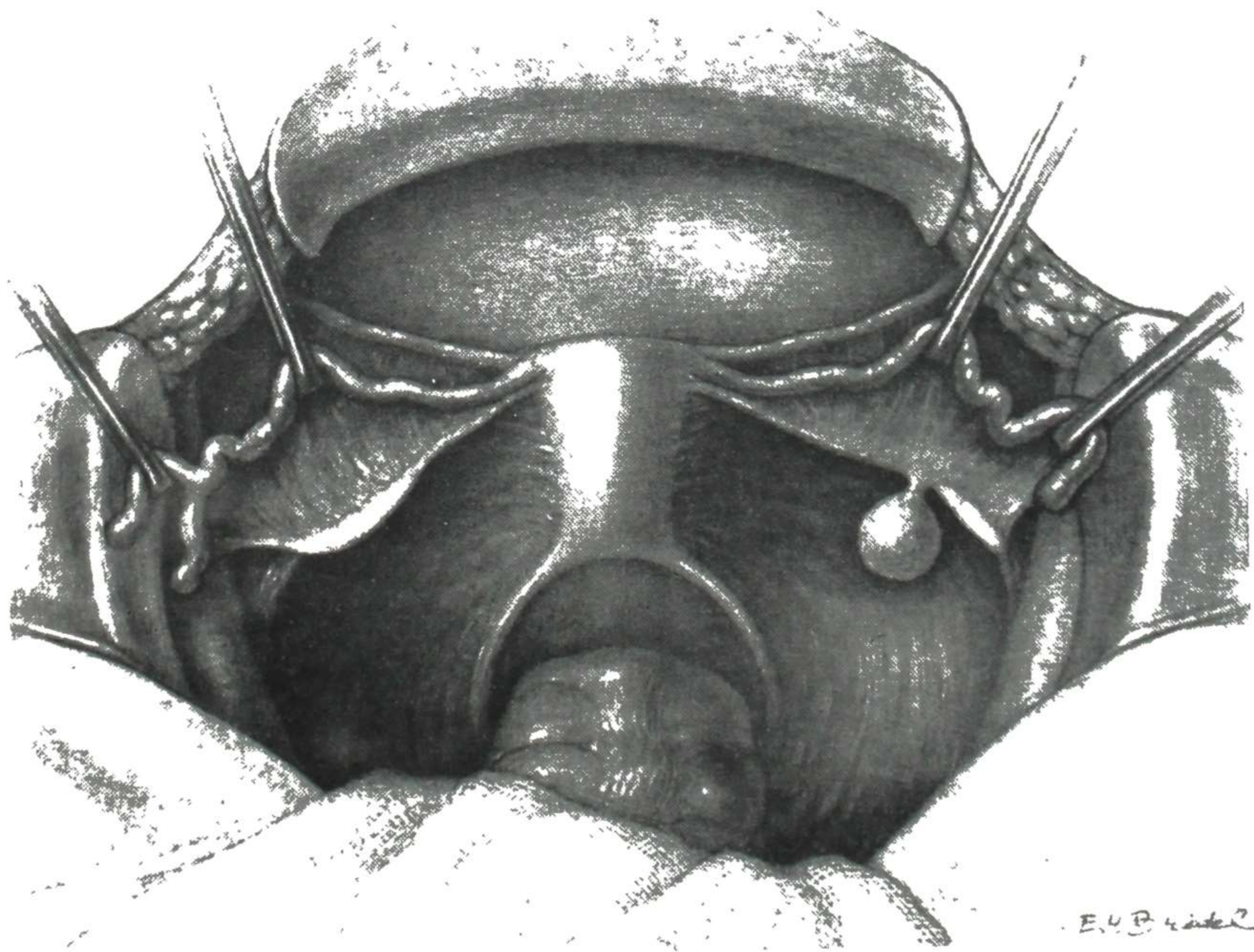
Fig. 959.—Laparotomy findings in hermaphrodite.   Note infantile uterus and tubes, ovarian thickenings bilaterally, and testis on right.   (From Stromme: Am. J. Obst. & Gynec., June, 1948.)

though there is considerable dispute among authorities concerning some. Over forty cases have been recorded in which, among other anomalies, there were glands that on microscopic examination presented some of the characteristics of both ovary and testicle. But that condition does not constitute a double set of glands and excretory ducts. In Fig. 959 is shown a sketch of the conditions found in a case reported by Stromme.

A **pseudohermaphrodite** is an individual of one sex presenting some of the local characteristics of the other sex. Many such cases have been recorded and not a few of them have presented a most difficult problem in regard to the diagnosis of sex. Neugebauer was able to collect 942 cases of pseudohermaphroditism. In at least 41 of the pseudohermaphrodites the true sex was positively determined only after abdominal section, though in only four

Fig. 960. Fig. 961.

Fig. 960.—Male pseudohermaphroditism. The appearance of the external genitals in marked hypospadias.

Fig. 961.—A section explanatory of Fig. 960. *B*, Bladder; *R*, rectum; *P*, penis with lower urethral wall absent; *H*, abnormal condition constituting hypospadias and requiring a careful examination to determine the sex of the child; *X*, sinus pocularis, enlarged and opening on perineum, and likely to be mistaken in the newborn for a vagina.

cases was the operation undertaken specifically for diagnostic purposes. Numerous cases are recorded in which the individual dressed and lived for many years as a man or as a woman, and then ascertained that the real sex was the opposite one. The most celebrated case, perhaps, is that of Carl Hohmann, a masculine pseudohermaphrodite, who from infancy to the age of forty-six years was considered a female and lived as such. The true sex being then ascertained, he assumed male attire and married as a man. The space available is not sufficient to permit the subject of pseudohermaphroditism to be taken up in an extended way. It is sufficient to mention some of the more practical points.

When a child presents any anomaly of the genital organs, a most careful examination should be made and all the possibilities considered, in order to determine positively the real sex. Most of the pseudohermaphrodites are really males (have testicles in the abdomen or scrotum), the resemblance to the female external genitals being due to some form of hypospadias accompanied with an abnormal opening or pocket that is mistaken for a vagina (Figs. 960 and 961). The principal anomaly in female pseudohermaphrodites, that causes some resemblance to the male sexual organs, is hypertrophy of the clitoris, accompanied with adhesions of the labia minora or labia majora over the vaginal opening, or with imperforate hymen (Fig. 926), or with labial hernia, or hydrocele or other labial swelling covering the vestibule.

In some cases the positive determination of the sex is very difficult and may even be impossible except by abdominal section. It used to be thought that because most of these cases proved to be male as far as the gonad was concerned, it was best, in case of doubt, to classify the case as male until proved otherwise. In view of the fact that most of these male hermaphrodites are inadequately equipped to carry out the masculine marital role and have a female psychologic make-up and tendencies, and because by rather simple surgical procedures a vagina can be formed, fitting these patients for satisfactory female careers, it would seem the wiser course to diagnose them as female until future events or desires indicated the necessity of changing the decision.

The value of endocrine studies in these cases as a factor in classification has proved to be disappointing, as both androgenic and estrogenic hormones are present, and also other organs, especially the adrenals, may produce the sex hormones.

In designating the type of pseudohermaphrodite, if the external genitals are of the male type but ovaries are present, it is called pseudohermaphroditismus femininus or gynandry; whereas if the external sexual characteristics have a female aspect but testes (usually undescended) are present, it is designated as pseudohermaphroditismus masculinus or androgyny.

The problems involved in classification and treatment of these cases can best be elucidated by giving the details of a case reported by H. S. Crossen:

About the first of September, 1938, a young woman was sent to me for construction of a vagina. (Fig. 962 shows the patient as she came for consultation.) She was twenty-eight years of age, and had never menstruated, though there had been some irregular bleeding when she was about twenty and again at twenty-six. On examination, I found the genital organs identical with those of a male pseudohermaphrodite. (The conditions are shown diagrammatically in Figs. 960 and 961.) There was the small hypospadiac penis, and back of that a vestibule with two openings, the one in front being the urethra, and the one a little farther back, an enlarged sinus pocularis. The testicles were in the groins.

. The general build was masculine, with narrow hips compared to the shoulders (Fig. 963). There was marked hair growth, with masculine distribution. Also, the patient had a beard which required regular shaving. There was more breast tissue than is ordinarily found in the male (Fig. 964). The left testicle was lower in the groin than the right, extending down into the upper part of the left labium majus (Fig. 965).

In such a case, of good development of instincts and mental make-up and poor development of physical structures, it seemed to me that the individual should be classed on

the side of the well-developed set of phenomena. Hence, I felt that the patient should be considered as primarily and essentially a female, and that our advice and treatment should be directed accordingly.

Now, could any substantial support be found for thus classifying and treating as a female, a patient with testicles and no ovary? The decision was a serious matter, for on it rested the direction of the future life activities of the individual. Also, the decision had to be made promptly, as the patient was recovering from the abdominal exploration and was about ready for the further surgical work required.

In the short time available, I found records of seven comparable cases, that is, of cases in which predominant female sex desires and preferences persisted in the presence of testicles without an ovary. Of course, there are many other reported cases of this type, but these seven cases had been handled in recent years, under the present fund of knowledge concerning endocrines and sex determination, and hence their handling was studied with particular interest.

Fig. 962.—Another pseudohermaphrodite, as the patient appeared for examination.

In these seven cases, the absence of ovaries was confirmed by abdominal exploration in five, and seemed fairly certain in the other two. The testicles were removed in six cases, and in the other case they were shifted from the groin to inside the pelvis. The hypertrophied clitoris was removed in four cases. In all of the patients operation was followed by improved social and sexual adjustment and continuation of normal libido. The essential details of these reported cases applying to our problem, were briefly as follows:

Mishell (Case 1): Patient, aged 35, was of feminine build, but had never menstruated. She came for treatment for tender lumps in the groins. Examination showed double inguinal hernia with a testicle in each. External genitals were normal, with vagina represented by a small canal three inches long ending bluntly with no cervix.

Abdominal exploration showed no ovaries, tubes, or uterus. The testicles were removed, and the hernias repaired. Improved adjustment. Patient returned to her work. Normal libido.
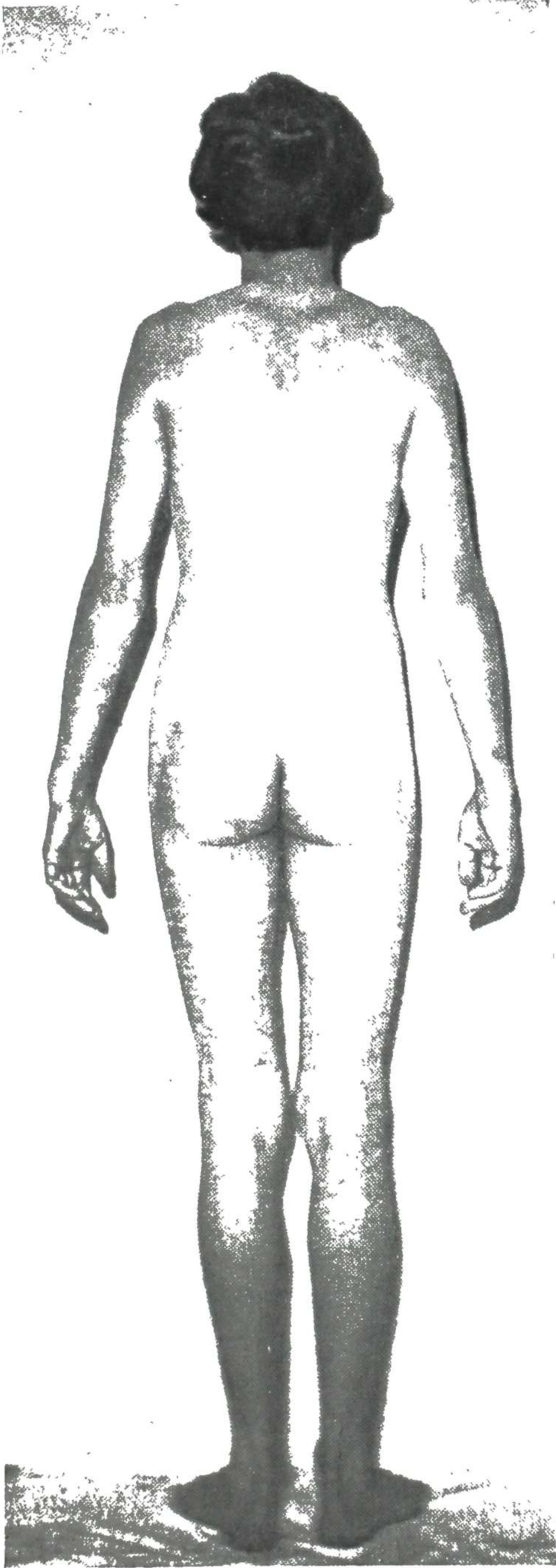
Fig. 963.

Fig. 964.

Fig. 963.—Showing the male type of body form, with broad shoulders and narrow hips.
Fig. 964.—There was more breast tissue than in the male.

Mishell (Case 2): Sister of preceding patient, aged 23, feminine build, complained of tender lumps in groins. Abdominal exploration showed no ovaries, tubes, or uterus. Testicles were removed. Improved adjustment and patient continued with good health. Headache which had troubled her disappeared after the operation.

Fig. 965.—The external genitals, showing marked hair growth, a testicle in the left labium majus, an enlarged clitoris and the perineal opening leading into a short vagina (or an enlarged sinus pocularis).

Mishell (Case 3): Sister of the preceding, aged 32, had lumps in the groins and had never menstruated. Examination showed the same condition in this sister as in the other two. Feminine build, good breasts, no hirsutism, and instincts and feelings all feminine. The only thing special was that she became gray in childhood at the age of nine. The patient was well-adjusted, emotionally stable, had no complaint, and no operation was required. This was one of the two cases in which the absence of ovaries was not confirmed by abdominal operation, but careful pelvic palpation along with the similarity to the other two sisters excluded ovaries with fair certainty.

Rubovitz: Patient, aged 39, masculine build, beard, testicles in groins, hypertrophied clitoris, short vagina, came complaining of severe libido and painful erections. The testes and the hypertrophied clitoris were removed, and the short vagina lengthened. There was improved adjustment and a normal libido. The relief from the annoying erections was probably due more to removal of the enlarged and hypersensitive clitoris than to removal of the testicles, for as pointed out later the removal of the testicles seems to exert no influence on the sexual desires and responses of these patients. This is the other case in which the absence of ovaries was not confirmed by abdominal operation. But by deep palpation and the use of pneumoperitoneum, it was felt that ovaries were excluded with fair certainty.

Wharton: Patient, aged 18, was of masculine build from the waist up and feminine build from the waist down. Had a beard. There were bilateral inguinal hernia, hypertrophied clitoris, and short vagina. On this diagnosis, the troublesome hypertrophied clitoris was removed and the hernia operation begun. In the hernial sac a testicle was found. An incision on the other side showed another testicle. The incisions were then closed, and later it was explained to the patient that a serious mistake had been made in amputating the supposed enlarged clitoris, which was in fact a penis, and that she was not a female but a male with two testicles. But the patient took quite a different view of the situation. She stated that no mistake had been made in amputating the enlarged clitoris, that she knew she was a woman and that she intended to live as such, and insisted on removal of the testicles. The testicles were finally removed, and abdominal exploration showed no ovaries. Improved adjustment. Normal libido. The patient married and sexual intercourse was satisfactory on her part and also on the part of the husband, except that the vagina was short. It was lengthened later.

Young: Patient, aged 21, masculine build, but no beard. Lumps in the groin, no vagina. Patient was engaged to marry. Abdominal exploration showed no ovaries, tubes, or uterus. A vagina was constructed and the inguinal testes were put back in the pelvis instead of being removed. Improved adjustment. Normal libido.

Novak: Patient, aged 19, masculine build, beard, hypertrophied clitoris, short vagina. In this case pelvic palpation showed bodies in the position of the ovaries, and about that size. Abdominal operation showed these bodies to be testicles in the usual position of ovaries and with a rudimentary broad ligament, but no ovaries, tubes, or uterus. The abdominal testes and the hypertrophied clitoris were removed. Improved adjustment. Normal libido. The vagina is to be lengthened later.

Our Case (for comparison): Patient, aged 28, masculine build, beard, testicles in the groins, short vagina. Came for construction of vagina. Abdominal exploration showed no ovaries, tubes, or uterus.

It was clear then that those who had already struggled with the problem of the cases of this type had reached the same conclusion I had, namely, that the patient should be treated as a female. Some had reached this conclusion in the primary study of their patient and others had been forced to it by later developments which confirmed and emphasized the predominance of the female element in the personality.

Having classified the patient as a female, with the right to live as such, the next step was to plan treatment to help as much as possible in that direction. The patient's two complaints were: first, the hair on the face which required frequent shaving and, second, the smallness of the vagina. So the two problems were to lessen the facial hair, by lessening the masculinity, and to lengthen the vagina. To accomplish these things, a combination treatment was planned consisting of (a) removal of the testicles, (b) administration of estrin preparations, and (c) stretching treatments for the short vagina.

Accordingly, I removed the testicles, doing the work under local anesthesia and checking each one with frozen section examination before removal, to exclude herniated ovary or ovotestis from removal. Later, Dr. Hobbs, in charge of the Laboratory, made a careful microscopic study of the testicles and there was no indication of ovarian tissue anywhere. As usual with retained testicles, there was no spermatozoa formation. At the preceding abdominal exploration, Dr. Sanford made a critical palpation of the kidney areas and could find no indication of adrenal tumor.

Following the operation the vagina was systematically stretched by having the patient use graduated dilators. Estrogen was administered orally to increase "her" feminine attributes.

An important point in taking care of such a patient is to avoid terms or expressions which may disturb her psychologic balance by making her uncertain as to her sex. All records and explanations and reports should be made to conform to the correct primary sex, as worked out by careful study of the case. The patient is already disturbed by the malformation which she wishes corrected, but as a rule she has no thought that she may not be a woman, and it is strongly inadvisable to put her further adrift on the sea of uncertainty by branding her as a male according to the old superficial structural classification.

This patient was married a year later and has now been happily married for twelve years; she states that intercourse is very satisfactory and usually she experiences an orgasm.

Since report of this case in 1939 the importance of careful study of the psychologic aspects of each case has become generally realized. This has been emphasized by Novak.
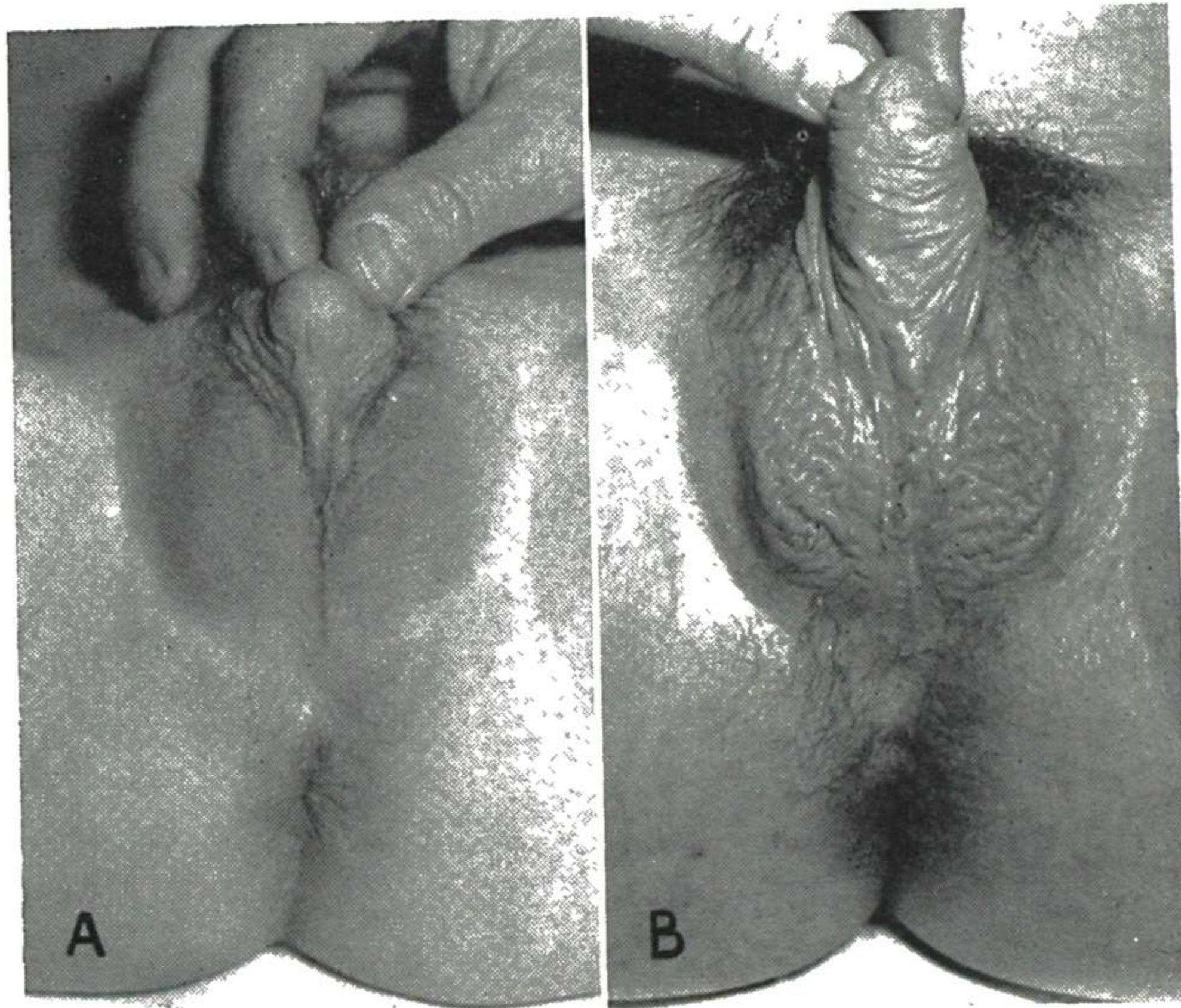
Fig. 966.—External genitals in a case of hypospadias: *A,* preoperative, age 2 years; *B,* postoperative, age 3½ years. (From Hinman: J. A. M. A., June 2, 1951.)

Recently Hamblen et al. made a careful endocrinological and psychosomatic study of eleven male pseudohermaphrodites and concluded that castration was indicated for the following reasons: (1) It eliminated the participation of the testes in the abnormal steroid metabolism. (2) Estrogenization was facilitated. (3) Neoplasia of the cryptorchid testes was avoided. (4) The patient felt more secure with the undesired male gonad removed. They used estrogen postoperatively to increase and speed up feminization. This plan was used in our case reported above, but there are some men, including Novak, who feel that it may be better to retain the testes and, if necessary, replace them in the abdomen, because of their general metabolic effect as well as their endocrine effect on libido.

The question of surgical reversal of sex in female hermaphroditism has been thoroughly discussed by Hinman in a recent article. He found that female hermaphroditism from adrenal hyperplasia is usually a progressive

masculinizing disorder. He advises deferring clitoridectomy until puberty so as to be certain which direction sexual development will take. In a later article he collected 149 cases of female hermaphroditism due to fetal adrenal hyperplasia. He feels that the progression toward masculinization can be

Fig. 967.—Taken at operation. Showing uterus, tubes, and gonads present in the left inguinal canal, exposed through a hernia incision. (From Pratt: Am. J. Obst. & Gynec., November, 1940.)
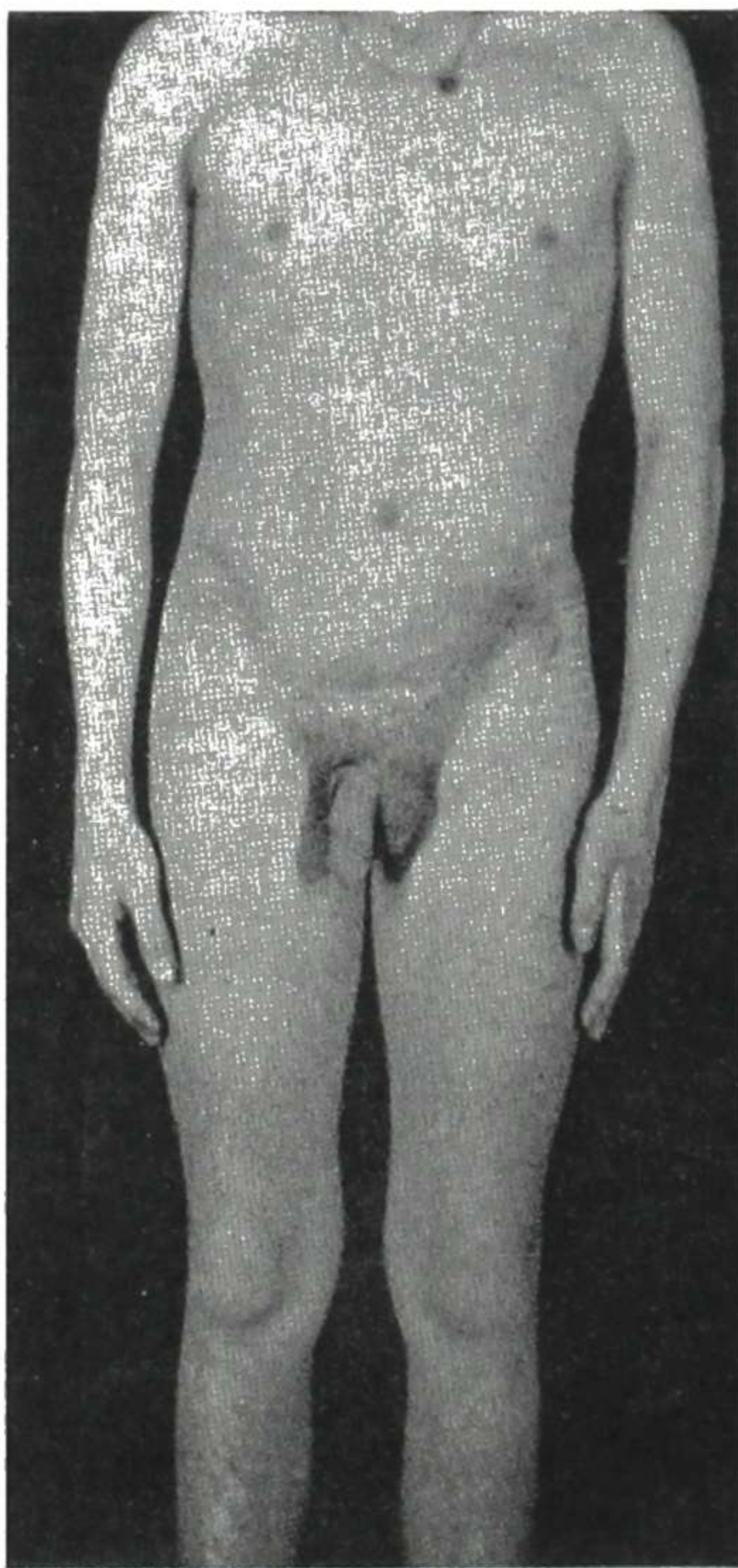
Fig. 968.—Postoperative. (Same case as in Fig. 967.) Showing normal male torso, extremities, and genital organs. The discoloration of lower abdomen and groin is due to antiseptics and dressings for operation. (From Pratt: Am. J. Obst. & Gynec., November, 1940.)

detected in childhood by increased bone age, advanced secondary sex characteristics, and an elevated 17-ketosteroid excretion. The decision as to surgical correction by correction of the hypospadias is made after considering all the factors in the individual case; Fig. 966 shows a case in which this was done at the age of 2¾ years. In addition to the operation this child was given desoxycorticosterone because of adrenal insufficiency.

There are a number of reports of well-developed male hermaphrodites in whom female structures are found in an inguinal hernia; one reported by Pratt is shown in Figs. 967 and 968.

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Chapter 13
MENSTRUAL DISTURBANCES

DISTURBANCES OF FUNCTION

In taking up disturbances of function in this and the succeeding two chapters, we shall consider not only those disturbances which are designated as "functional" because no organic lesion is apparent, but also the disturbances of function due to various organic diseases—that is, all "disturbances of function," whether or not accompanied by evident organic disease. These conditions are, of course, only symptoms. They are not diseases and must not be taken to constitute a diagnosis. They are only indications of some disease, and the physician must determine the nature of that disease by further investigation.

A word concerning the psychosomatic aspects of functional gynecologic disorders is indicated. As Mandy et al. so aptly expressed it, a large proportion of women who seek aid for female trouble are in reality troubled females. Due to the delicate balance and integration of the psychologic and physiologic processes of the reproductive system, one can assume that almost every woman will at some time in her life develop a psychosomatic pelvic disturbance. These disorders are expressed as menorrhagia, amenorrhea, dysmenorrhea, frigidity, and others. The exact mechanism by which these changes are produced is not known, but it is probably mediated through nerve fibers entering the pituitary through the hypothalamus, and through this neurohumoral mechanism the secretions of the anterior lobe of the pituitary are affected. Greer has shown that the thyrotropic "growth factor" is dependent on the continuity of the hypothalamus though the "metabolic factor" is independent of this hypothalamic influence. In Chapter 11 a table of the psychodynamics of functional pelvic disorders, proposed by Mandy et al., is given. Treatment of the obstinate case is in the realm of psychiatry. O'Neil discusses the psychiatric treatment of twelve cases of uterine bleeding associated with tension states. An excellent summary of diagnosis and treatment of anxiety states, for use by the general physician, is given by Terhune.

In Chapters 13 to 15 the disturbances of function will be taken up in the following order:

Menstrual Disturbances
Sterility and Sexual Disturbances
Miscellaneous Disturbances (including those of the Climacteric)

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MENSTRUAL DISTURBANCES

In considering disturbances of menstruation we shall take them up in order as follows:

Menorrhagia, Metrorrhagia, Irregular Menstruation, Precocious Menstruation, Vicarious Menstruation, and Intracyclic Bleeding.

Absence of Menstruation (Amenorrhea).

Painful Menstruation (Dysmenorrhea), Premenstrual Tension, Menstrual Headache, Intermenstrual Pain, Menstrual Pruritus.

MENORRHAGIA AND METRORRHAGIA

When a patient complains of uterine bleeding, it is often a question at first whether the bloody discharge is excessive menstruation or bleeding from some other cause. A considerable period of investigation and treatment may be needed to determine this point. The pelvic examination may not settle it, for, even if no palpable lesion is found, there may still be a small submucous myoma or other nonpalpable lesion. Consequently, in the diagnosis and treatment of these cases in the office and at the bedside, the start is made with the combined groups represented by the bleeding patient.

In taking care of such a patient, treatment is given, of course, to stop the blood loss while investigating its cause. The response to treatment aids somewhat in further differential diagnosis and in determining what additional therapeutic measures are required. It is apparent, then, that the practical handling of these patients comprises a treatment-investigation program which checks the blood loss and, step by step, differentiates the underlying cause so that curative measures may be instituted.

TREATMENT-INVESTIGATION PROGRAM

The first interview and examination will identify those patients with an obvious lesion sufficient to account for the bleeding. The treatment for such lesions will be found in the appropriate chapters. For handling patients with no obvious lesion, it is convenient to group them into classes representing different age periods, as follows: (1) Infancy and childhood (ages one to ten). (2) Developmental period (ten to twenty). (3) Childbearing period (twenty to forty-five). (4) Involutional period (forty-five to sixty). (5) Senile period (beyond sixty).

Infancy and Childhood (Ages One to Ten)

The principal causes of bleeding in this age period are endocrine disturbance from withdrawal of maternal estrin at birth, constitutional precocious puberty, ovarian tumors exerting an endocrine influence (granulosa-cell tumors), pituitary or adrenal or pineal tumor, and rarely malignant growth in the vagina or ovary or uterus. Bleeding at birth or a few days thereafter, not due to birth injury, is caused by withdrawal of the maternal estrogenic hormone which the fetus has been receiving. This show of blood is of no clinical importance and requires no treatment.

In 1944 Novak called attention to the fact that precocious puberty in normal children is not as rare as formerly supposed, and he reported nine

cases, six of which were from his own practice. The lower normal limit for the onset of puberty is usually considered to be eight years of age, but in all nine cases reported by Novak the age at onset of the menses was below this limit. The ages of his patients being 15 months, 2 years, 2 years 8 months,

Fig. 969.
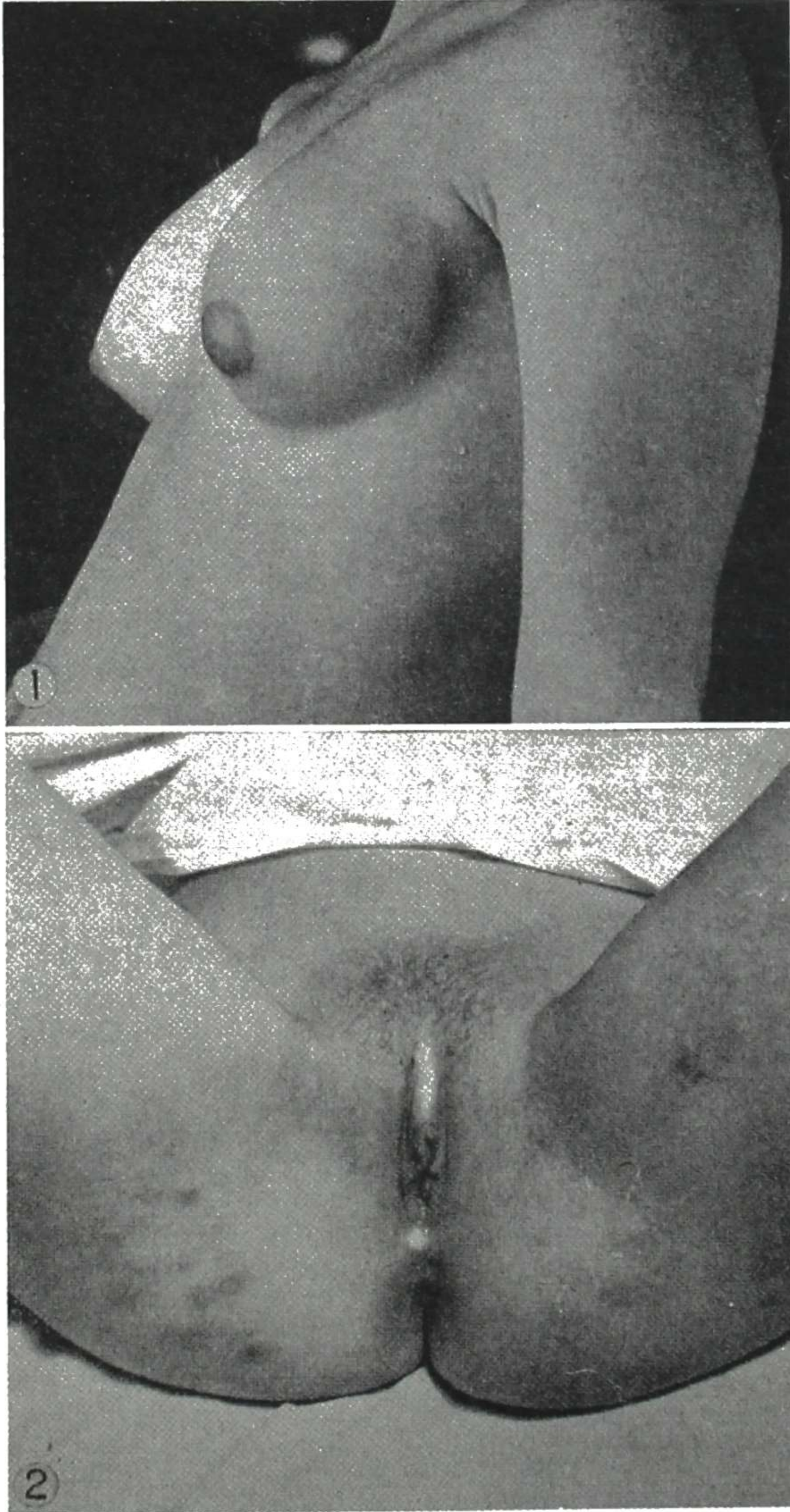
Fig. 970.

Figs. 969 and 970.—Premature sexual precocity. Girl aged 4 years, 11 months. (From Karnaky: J. Clin. Endocrinol., April, 1945.)

4, 4½, 6½, 7 (two cases), and 7½ years. Figs. 969 and 970 show the development in a 4-year 11-month-old girl reported by Karnaky, and three additional cases were recently reported by Mason; additional references are given in Chapter 11 under granulosa-cell tumors.

These patients require no active treatment, but advice to the parents and other adults who have contacts with the child, on the psychological problems

involved, is very important in order to avoid the development of abnormal complexes. In this constitutional type of early puberty, not only the menses but also ovulation may occur, and the possibility of pregnancy must be kept in mind.

The diagnosis of the constitutional type of precocious puberty is made by ruling out the other causes of this condition. These are granulosa- and theca-cell tumors, adrenal tumors, pineal tumors, and the cerebral type. This latter type is due to lesions involving the floor of the third ventricle and the hypothalamic area. A recent case of the Albright syndrome described by Baskin and Kennedy belongs in this cerebral group.

Local conditions in the vagina such as polyp, foreign body, or tumor can easily be ruled out even in infants by examination of the vagina with a Kelly endoscope.

From the general examination one can tell if the child belongs in the endocrine group of cases found in adrenal, ovarian, pituitary, and pineal tumors. The differential diagnostic points are given in Chapter 2, and suggestions for the examination will be found under the details for the next age period.

The treatment consists of general supportive measures while the underlying cause is being investigated. After the cause of the bleeding in the case is determined, treatment is given for that particular disease as outlined in the appropriate chapter. Vaginal bleeding in young girls which cannot be accounted for by some general blood dyscrasia or other evident lesion calls for a thorough investigation, because a pelvic tumor is the cause of the bleeding in a large proportion of the cases of this age group. This investigation should include, when necessary, pelvic examination under anesthesia and curettage, with microscopic diagnosis of the tissue removed.

Developmental Period (Ten to Twenty)

This is the developmental age as far as the functions of the genital tract are concerned. The causes of bleeding in this age period are endocrine disturbances, blood dyscrasias, inflammatory lesions, pregnancy complications, ovarian tumors, uterine myomas, and malignant disease—the relative frequency of occurrence being about in the order given.

The first step in the investigation-treatment program in these cases is to obtain in the history an accurate record of certain items of special importance in the differentiation, as follows:

History items of special importance.
  a. Menses—age of onset, regularity, duration, amount.
  b. Weight—loss or gain, with time involved.
  c. Hair—texture, distribution, premature graying, or undue falling out.
  d. Headaches—location, type, duration.
  e. Vision—glasses necessary, or other disturbance.
  f. Gastrointestinal symptoms.
  g. Nervous symptoms—irritability, depression, crying spells.
  h. General symptoms—Does patient tire easily? Is she sleepy most of the time? What are her habits of sleep, exercise, work about the home, study, recreation at home, vacation activities?

Examination items of special importance.
  a. Type of build—measurements symphysis to floor, symphysis to crown, span from finger tips to finger tips.

b. Secondary sex characteristics—hair distribution and texture, breast development, vulvar hair growth and development of parts (labia, clitoris).

c. Lean or fat. If fat, note distribution.

d. Blood pressure and pulse.

e. Findings in the abdominal, rectal, and rectoabdominal palpation.

Having obtained the items of information and recorded them for study, the physician is in a position to begin recognition of the general type of disturbance, which recognition will indicate the next step in the diagnostic-therapeutic program. The general groups to be considered in these bleeding patients of the developmental age, are (1) the blood dyscrasia cases, (2) the general disease group, (3) the pelvic lesion group, and (4) the endocrine cases.

1. Blood Dyscrasia Group. Uterine bleeding may be due to the condition of the blood without any local disease. It is surprising over how long a period patients will be given endocrine and other treatment before having a blood examination, which reveals the serious disease behind the symptomatic uterine bleeding. To mention this is sufficient to call attention to the importance of prompt investigation of the blood condition in bleeding cases, so that any serious disorder in the blood-making organs will be discovered early.

2. General Disease Group. Other serious general diseases, such as pulmonary, gastrointestinal, kidney, and cardiovascular, are to be eliminated, and in this age group it is ordinarily advisable to make that elimination before subjecting the patient to vaginal examination.

3. Pelvic Lesion Group. The patient may have a uterine myoma or an ovarian cyst or one of the special tumors with endocrine influence (granulosa-cell tumor) or one of the rare malignant tumors of adolescence (teratoma, sarcoma). Any one of these conditions may cause sufficient disturbance to result in a bloody discharge.

Some differentiation information in this direction has been secured in the general examination, which in these patients should include careful abdominal palpation and rectal and rectoabdominal palpation. The latter will show if there is any mass of considerable size in the pelvic interior or any area with undue tenderness. Culdoscopy is also helpful.

4. Endocrine Group. If there is no evidence placing the patient in one of the three groups above mentioned, we assume for the time being that she belongs to the endocrine group, and proceed accordingly.

ENDOCRINE CASES

In order to understand therapy in the endocrine group it would be well to review the mechanism of normal menstruation given in Chapter 1.

Interest in the anovulatory cycle was stimulated by the work of Corner and of Hartman who proved that in monkeys menstruation occurred with and without ovulation. When the cycle was anovulatory, there were no corpus luteum and no endometrial progestational changes; when ovulation occurred, these endometrial changes were present.

Anovulatory menstruation is common in the adolescent before the initiation of the regular ovulatory mechanism, hence some irregularity in time and amount of flow is to be expected during the first year or so of menstrual life and no special treatment is required unless this persists for several years or the bleeding is so excessive as to cause anemia or interferes with the child's health. Even when the menses become normal, the cycle may be disturbed by changes in environment and psychic upsets. Winther found that of 19,283 women entering the University of Minnesota from 1935 to 1945, 5,210 consulted the gynecologic department of the Student Health Service. Irregular bleeding was the chief complaint in 32 per cent of these. Many of the cases of this type will clear up spontaneously when they become adjusted to their new surroundings and situation, and after ruling out other causes for bleeding the physician should take time to reassure them that there is nothing seriously wrong.

Pathology.—The ovarian findings in these cases of anovulatory bleeding are an absence of ovulation causing a persistence of unruptured follicles and an absence of corpora lutea. The failure of the ovulatory mechanism is not clearly understood. Hofbauer feels it is due to an overactivity of the anterior pituitary; others feel that it is due to an underactivity of the anterior pituitary; and others, including Burch, feel that ovarian failure to respond to the gonadotropin hormones is responsible.

In the majority of the cases the endometrium is hyperplastic with no evidence of progestational changes, though some show a normal proliferative endometrium. Experimentally hyperplasia has been produced in normal and spayed rodents by injection of anterior pituitary extract by Hofbauer, and by estrogen injections by Burch and others. Hyperplasia of the endometrium was produced by estrogen administration in monkeys by Zuckerman and Morse, and in the human being by Kaufman and by Werner and Collier. Irregular shedding of the endometrium is discussed under the next age group.

Diagnostic Tests.—Several methods for determining whether or not ovulation has occurred are now available, and which should be used depends upon the facilities at hand. The oldest reliable clinical test is the premenstrual biopsy. A good gynecological pathologist can tell whether ovulation has occurred and usually can estimate the degree of progesterone stimulation, by the degree of the progestational changes, in cases where ovulation has occurred. In well-equipped laboratories trained in the vaginal smear technique the exact day of ovulation can be determined as well as the degree of hormonal stimulation (see Fig. 103). A recent summary of this subject is given by Bonime. The use of pregnanediol determinations in the urine for this purpose is advocated by de Watteville, using a simple test which is a modification of the Astwood-Jones technique. He concludes that the presence of pregnanediol in the urine excludes gross sex hormone disorders of ovarian or pituitary origin.

Treatment.—Before starting on specific types of therapy it is well to mention several **general principles** controlling the order in which treatment methods should be used. First in importance is the amount of flow. If this is excessive and the blood loss is marked, curettage will be the first step. After the bleeding is controlled, then investigation may be carried out to determine treatment. (Fatal menstrual hemorrhage has been reported in young girls.) Next the age of the patient is important. For instance, we prefer conservative treatment in young women, whereas in women over forty-five radiation may be the method of choice. Last, the economic status of the patient will arbitrarily limit the therapy to medicine which the patient is able to afford.

The **order of treatment,** then, in young girls and women in childbearing age will be about as follows, with variations as dictated by the above-mentioned conditions:

1. NUTRITION.—The importance of nutrition in relation to endocrine function is now well established, and hence the diet should be high or low in calories depending upon the case. A high protein diet is important in reducing the clotting time, and milk, cheese, and other dairy products furnish calcium which is important in the blood-clotting mechanism. The vitamins of

special importance in functional bleeding are vitamin C, vitamin B complex, and vitamin K. In most cases it is well to start the patient on a preparation containing all of the vitamins, minerals, and trace elements, for the importance of these nutritional elements is now recognized, though their action is still not completely understood. Junghans was able to control menorrhagia in 33 of 35 patients by intramuscular injection of 50 mg. of ascorbic acid (vitamin C) twice daily.

2. THYROID.—Thyroid therapy should be given when the basal metabolism indicates a need for it. The basal rate is not always accurate as a guide to therapy, but usually a grain of standard thyroid for a −10 of the basal rate will be adequate. If symptoms persist, the dose may be increased cautiously, using the patient's feelings and the pulse as a guide.

3. ERGOTRATE.—In atonic individuals the bleeding may be due to a lack of uterine tone, and these are the cases most frequently helped by ergotrate. The firm contraction of the uterus, by compressing the deeper circulation, diminishes the volume of blood flow through the uterus and thus the amount of blood loss.

4. NONENDOCRINE THERAPY.—Snake venom has been used successfully in the treatment of functional bleeding by Peck and Goldberger.

They reported relief in 17 of 20 women treated, and state that the expense of therapy is considerably less than it is with hormone therapy. The venom has a direct effect on the walls of the small blood vessels, making them more resistant to bleeding. The improvement in these cases extended from two months to four years.

Method.—Moccasin venom in 1:3,000 dilution (prepared by the Lederle Laboratories) is used. Daily doses are given subcutaneously, starting with 0.5 c.c. and increasing to 1 c.c. by the third dose. If the bleeding is very profuse, 1 c.c. is given twice daily until the bleeding is controlled, then two to three times a week for three menstrual periods.

As much treatment as possible should be given during the first ten days, for patients develop a sensitization to the venom and must be desensitized before continuing therapy. Peck has been able to separate the antigen of the venom from the factor active in controlling bleeding so that the undesirable sensitization action is eliminated.

In 1949 Allen and his associates described an inhibitor to blood clotting in certain hemorrhagic conditions which could be neutralized by protamine sulfate and toluidine blue. The presence of this unknown inhibitor can be determined by protamine titration, and variations occur with bleeding episodes. At first it was thought that this varied with the platelet count and prothrombin time, but this has not proved to be the case. It is affected by heparin but this is evidently not the principal factor as endogenous compounds not related to heparin will produce an elevated protamine titration.

Rumbolz and his associates tested protamine sulfate and toluidine blue in 25 cases of menometrorrhagia and obtained relief in 18 cases. The protamine titration taken at the period time was increased in 23 of these patients. Most of the patients were given 100 mg. in capsules twice a day for four days when toluidine blue was used, and 50 mg. of protamine sulfate intramuscularly daily for four days when this therapy was used. Priddle, in the discussion of this paper, suggests using this therapy empirically in cases where there is no evident gynecological cause for the bleeding and states that it should be repeated for three or four periods if necessary.

5. HORMONE THERAPY.—The bleeding may be caused by abnormal activity of any of the endocrine glands concerned with pelvic function: pituitary, thyroid, ovaries, and, probably, the adrenal. The importance of thyroid in all of the functional diseases is well established but the mechanism of its action is not clearly understood. Goldsmith et al. found that in a group of ten unselected myxedematous premenopausal women, endometrial biopsy demonstrated ovulatory failure in seven and the eighth showed an inadequate corpus luteum effect. In 17 of 18 premenopausal patients with thyrotoxicosis there were complaints of amenorrhea or oligomenorrhea. The three with amenorrhea had evidence of ovulatory failure and hypoestrinism and two of the other patients had a hyperplasia of the endometrium; the remaining patients had no evidence of disturbances in the ovulatory mechanism in spite of the fact that their periods were not normal.

If diseases of the pituitary and adrenal cortex are ruled out and the thyroid function is brought up to normal, then by elimination one can assume that the disorder is one of imbalance of the ovarian hormones.

The hormones affecting ovarian balance are composed of three main groups:

A. Sex Sterols: progesterone, estrogens, and androgens.
B. Chorionic Gonadotrophins from pregnancy urine or pregnant mares' serum.
C. Anterior Pituitary Hormones from extracts (prolactin) or from castrate or menopausal urine in human beings.

A. Sex Sterols.—The treatment of uterine bleeding with the sex sterols is based upon the fact that administration of a large dose well above the threshold dose causes cessation of bleeding, and sudden withdrawal of the sex sterol, after a latent period, is followed by menstrual flow and desquamation of the endometrium. This has been termed an endocrine or chemical curettage, as it usually removes the abnormal endometrium, allowing the new endometrium to reform normally. The latent period for estrogens is approximately nine days, as seen in Fig. 971; for progesterone the latent period is two to four days; and for testosterone it is approximately fifteen days.

a. Progesterone (pregneninolone): Willard Allen gives the following outline of treatment of functional bleeding with progesterone:

"The satisfactory methods of treating functional bleeding utilize the female sex hormones and fall into two general classes. The rationale behind each is actually quite different. The primary disturbance in the ovary leads to the production of too much estrogen for too long a period. A better way of stating the problem is to say that the natural sequence of estrogen followed by estrogen and progesterone does not occur. The disease can, therefore, be looked upon as one due to hyperestrinism, but not necessarily implying a higher production of estrogen than normal, or as one due to a lack of progesterone. Either concept makes possible rational treatment with the sex hormones. The use of progesterone is the most logical because the disease is due to progesterone deficiency. Also, progesterone tends to inhibit and alter the effects of estrogen.

"The effect of progesterone on the pituitary gland is uncertain, however. Testosterone can be used because it inhibits the stimulating effects of estrogen and also because it suppresses the pituitary and causes temporary inhibition of ovarian activity. The use of estrogens would seem paradoxical. If the disease is due to hyperestrinism, how could more estrogen be helpful?

"The fact remains that estrogen is beneficial although the exact explanation for the immediate effect remains unexplained. The later effects are more readily understood, however, since estrogen in suitable dose inhibits the output of follicle stimulating hormone and hence suppresses ovarian activity.

"The difference in these methods of treatment is simple. When using pure substitution therapy, progresterone, physiological doses are used. Whereas when using estrogen or testosterone, several times the physiological dose are necessary in order to produce pituitary inhibition.

"The details of the procedures which are ordinarily followed in the treatment of endometrial hyperplasia with the sex hormones are simple and straightforward. After bleeding has been in progress for two or more weeks, therapy is begun. If progesterone is to be used, 10 mgm. daily are given intramuscularly for six days. Bleeding ordinarily decreases during the period of injections, but there is almost always an exacerbation of bleeding beginning 36 to 48 hours after the last injection. This bleeding is due to progesterone-withdrawal and usually lasts from five to eight days. During this bleeding the hyperplastic endometrium is effectively desquamated. This corrects the pathological condition in the uterus and temporary relief is achieved. Fortunately, the result is frequently more permanent since many patients will have normal cycles for many months after a single course of treatment. The explanation for the appearance of normal cycles is rather obscure but it seems probable that progesterone in some ways alters for the better the pituitary-gonadal balance.
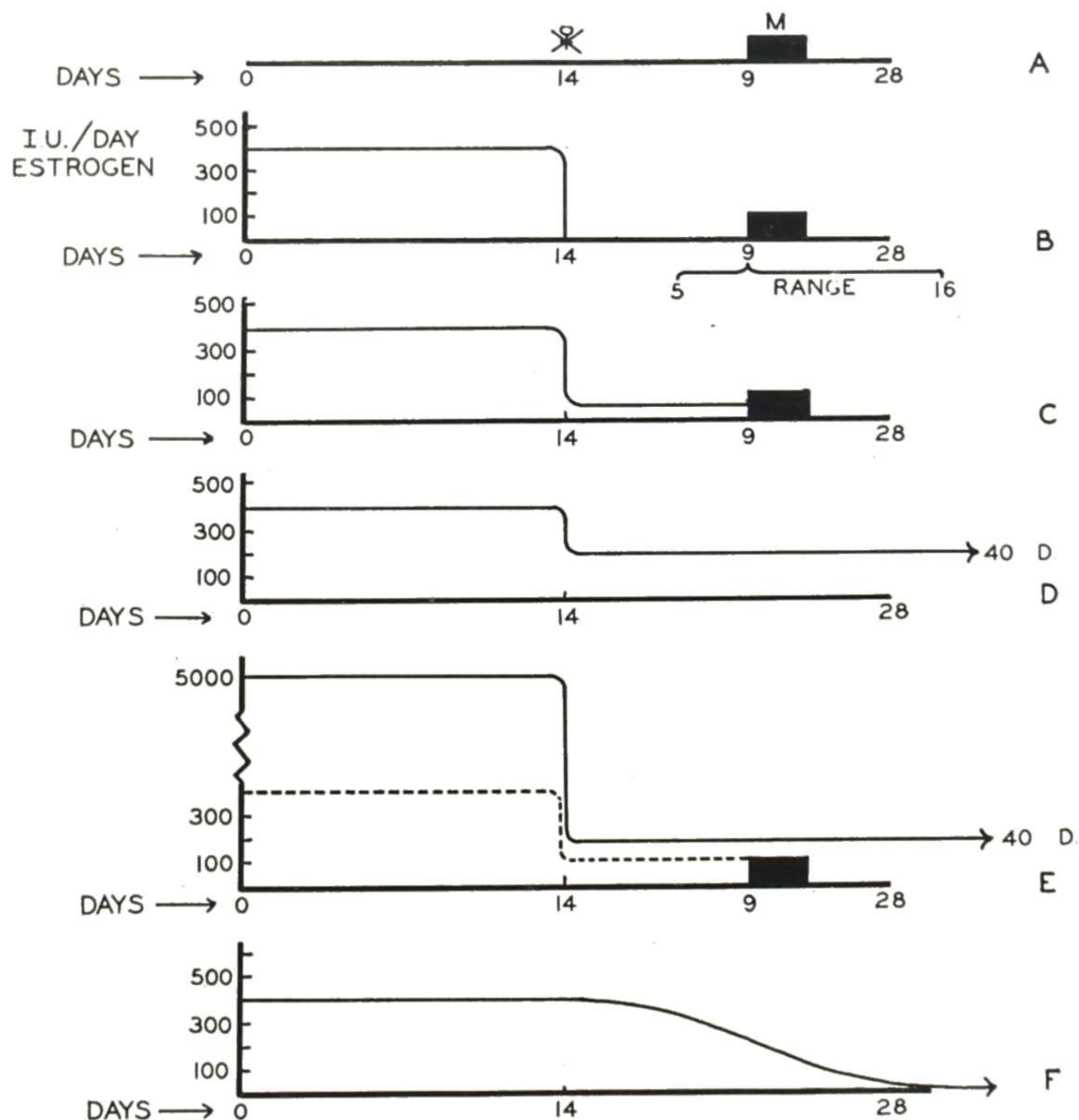
Fig. 971.—Estrogen-threshold and uterine bleeding, showing observations made over a period of years by a number of investigators, which have become common experience among workers in the field of experimental menstruation in monkeys. *A,* Estrogen withdrawal by means of castration only in adolescent or adult animal, not in infants or juveniles. *B,* Cessation of injections of estrogen. *C,* Bleeding will occur if the amount of available estrogen is reduced below the endometrial threshold. *D,* Bleeding can be prevented for variable periods of time even though the amount is reduced, provided it is above the threshold level. *E,* The quantity of estrogen originally given is not a factor, neither is the percentage of reduction of estrogen, nor is the amount of oil used as a vehicle important, provided that the endometrial threshold is exceeded (Zuckerman). *F,* Involution of the endometrium may occur without bleeding by the gradual reduction of estrogen (Hisaw). (From Engle: Am. J. Obst. & Gynec., October, 1939.)

"There are also other ways of giving progesterone. A larger dose of 25 mgm. may be given daily for three days, or the preparation for buccal absorption may be used at a higher level of dosage, usually 40-50 mgm. daily for six days. The closely related compound anhydrohydroxy-progesterone is equally effective at similar dosage levels. The end result is usually the same regardless of the method of administration."

Jones and Te Linde found that when oral anhydro-hydroxy-progesterone (pregneninolone) was used, a dose of 180 to 600 mg. was needed to control the bleeding.

b. Estrogens (estrone, estradiol, estriol, benzoated compounds, and stilbestrol): In view of the observation that excessive estrogen can cause endometrial hyperplasia and bleeding, it is not clear why the administration of estrogens stops bleeding. The effect of large doses is too prompt to allow for inhibition of the pituitary and, hence, it is thought to be due to a direct action on the coiled arterioles. The usual dose is ten times the physiologic dose. Hamblen has long been an advocate of estrogenic therapy. He uses either stilbestrol or, if the patient cannot take this, estrone sulfate. This latter is derived from the urine of pregnant animals and goes under the trade name of Premarin. The first step in the treatment is to stop the bleeding, and this is accomplished by giving diethylstilbestrol, 6 mg., or estrone sulfate, 7.5 mg., daily. The bleeding usually will stop within five days, but if it does not the dose is increased from 25 to 100 per cent. The required daily dose is then continued for twenty days, or until the bleeding occurs, and then the therapy is discontinued for five days. The dose is then reduced 50 per cent and the cyclic therapy (fifth or twentieth day) is continued for three periods, when a premenstrual biopsy is done to determine whether a progestational endometrium has been formed. The cyclic therapy as outlined sometimes helps to promote normal pituitary action. If there are no progestational endometrial changes, it is evident that ovulation has not occurred, so attempts are then made to cause ovulation by administration of pregnant mares' serum and chorionic gonadotrophin. The former is given 20 units from the fifth to the twelfth day and the latter 500 units from the twelfth to the twentieth day. If, after several trials, a premenstrual endometrium is not obtained, the ovaries are judged refractory.

The dosages advised by Karnaky, who was one of the originators of this type of treatment, are considerably higher than those advised by Hamblen. As mentioned above, the dose is ten times the physiologic dose necessary to relieve symptoms of estrogen deficiency seen in the menopause, and also the latent period from the cessation of treatment to the onset of bleeding is five to seven days instead of thirty-six to forty-eight hours as with progesterone.

Greenblatt recommended 20 mg. Premarin intravenously every six to twelve hours for three or four doses in severe uterine bleeding; following cessation of bleeding, oral therapy is instituted. In cases in which it is desirable to avoid heavy withdrawal bleeding, the dose is gradually decreased as follows: Premarin 1.25 mg. (or its equivalent) orally four times a day for five days, then three times daily for five days, then twice daily for five days, finally once daily for five days, and stop therapy.

C. Male sex hormone or androgens (testosterone propionate): The action of this hormone in controlling bleeding is thought by some to be an in-

direct one through the inhibition of the pituitary, while others, notably Sturgis, Abarbanel, and Nader, feel that the action is a direct one on the uterine muscle and on the muscle fibers constricting the coiled arterioles. The general action on the muscle inhibits rhythmic (estrin) contractions, thereby decreasing the volume of blood flowing to and through the uterus, and the local action stimulates the myometrial elements about the arterioles constricting them and thus helping to control the blood loss.

The method of treatment is 25 Gm. of testosterone propionate intramuscularly for four or five days or until the bleeding stops, then 25 mg. every other day until a total dose of 300 mg. has been given. With buccal therapy a dose of 10 to 20 mg. is given three times a week until the period is regulated. Signs of masculinization are a contraindication to this type of therapy.

Combined therapy with sex sterols has become popular in recent years. Greenblatt and Barfield obtained an arrest of bleeding in 95 per cent of their cases in twenty-four hours and in 100 per cent in seventy-two hours with the following therapy: Using a preparation containing progesterone 25 mg., testosterone 25 mg., and crystalline estrone 6 mg. (Tristerone, Wyeth), they give an initial dose; then, if the bleeding stops in twelve hours, they give another dose on the second and third days. If the bleeding does not stop, two doses are given the second and third days and single doses on the fourth and fifth days. Withdrawal bleeding occurs in one to six days after the last dose, after which cyclic therapy is started by mouth using either estrogens or progesterone or a combination of the two.

Bradbury, Long, and Durham have recently been able to produce decidual changes in normally menstruating women by giving a combination of 25 mg. of an aqueous suspension of progesterone crystals intramuscularly and an oral estrogen daily, started during the postovulatory phase of the cycle and continued until bleeding starts or until the period had been delayed two weeks. The daily dose of estrogen necessary to augment the action of the progesterone was found to vary with the type used: stilbestrol or equilin, 0.5 to 1.0 mg.; conjugated estrogens (Amnestrogen or Premarin), 2.5 mg. to 5.0 mg.; pure estrone sulfate was not effective in doses of 5.0 mg.

The danger of endogenous allergy to the steroid hormones has been emphasized by Heckel in an exhaustive review of the subject. He suggests that skin tests not only give a method of detecting the condition clinically, but also serve as a method for hyposensitization. According to Heckel, ovarian insufficiency in some cases seems to be due to an underlying allergy to the steroids, and in such cases he obtained an improvement of symptoms during hyposensitization by giving small intracutaneous doses of pregnanediol. He feels that this may prove to be a useful form of therapy in selected cases.

B. Chorionic Gonadotrophins.—a. The urinary gonadotrophins are usually obtained from human pregnancy urine, such as Antuitrin S, Follutein, A.P.L., and others. In experimental animals these preparations cause ovulation and luteinization of the follicle, and it was formerly thought that they produced similar results in the human being; but Hamblen and Ross and also Geist proved that in the human being this hormone caused destruction of the follicles but did not cause ovulation. Hisaw was able to prolong the corpus luteum function by large daily doses of the chorionic gonadotrophin in monkeys. In the

human being similar results have been obtained by the commercial products, but the large doses necessary caused severe reactions according to the report by de Watteville. In 1947, Willis Brown and Bradbury, using a special preparation of human chorionic gonadotrophin not available commercially, succeeded in prolonging the life span of the corpus luteum and delaying the menstrual period from twelve to nineteen days, by administration of daily doses varying from 5,000 to 20,000 I.U. The hormone was given daily from the twenty-fifth day of the cycle to the thirty-fourth day, and menses usually started two days after discontinuation of it. It is evident from this more recent work that the chorionic gonadotrophin exerts a luteotrophic effect on the corpus luteum, and hence it should be of value in the treatment of those cases in which the luteal activity is defective. Until less toxic products are available commercially, its clinical use is limited. Its use in smaller doses in combination with the lactogenic hormone will be discussed below under Pituitary Gonadotrophin. Hamblen's schedule for its use in combination with cyclic estrogen-progesterone therapy has been discussed under Sex Sterols.

b. Pregnant mares' serum is available commercially as Gonadogen, Equinex, Anteron, and others. When this chorionic gonadotrophin was first introduced, it was hoped that it would solve the problem of treatment in the cases in which ovulation was not occurring. Davis and Koff were able to cause ovulation at any time in the cycle in a group of normally ovulating women; however, further experience with pregnant mares' serum proved that it did not, as a rule, cause ovulation in patients who were having anovulatory cycles.

Hamblen feels that it has helped in some cases, and his dosage program has been outlined under cyclic sterol therapy above.

C. *Pituitary Gonadotrophins.*—a. The commercial pituitary gonadotrophins are obtained from animal pituitaries, either sheep, horse, or pig, and antihormone formation is the chief deterrent to their use in the human being. These antihormones not only antagonize the administered hormone but they also inactivate the patient's own pituitary gonadotrophins. Sevringhaus reported good result some years ago using Prephysin 50 to 100 I.U., from the fifth to the tenth day of the cycle, but there have been no recent reports on this product. Leathem and Rakoff reported excellent results in cases of sterility, amenorrhea, and functional bleeding using Synapoidin, and only rarely was there antihormone formation. The following is their method of treatment:

"When starting treatment it is desirable to be conservative in dosage until the patient's response to the product has been determined. Initial dosage should be from 0.5 to 1 cc. given intramuscularly. This may be increased to 2 cc. or more daily or two or three times weekly, depending on the response of the patient.

"In general, treatment courses should extend over a two or three week period with withdrawal periods of a week or longer, depending on the occurrence of menstruation and the patient's response to treatment."

Jungck and Willis Brown have recently described a method of obtaining human pituitary gonadotrophin from the urine of castrates and women in the menopause. They have proved that this preparation can be given over long periods of time without causing antihormone formation, but its value in stimulating ovulation in the human being has not been tested.

b. Lactogenic hormone, prolactin, Luteotrophin: The lactogenic hormone was the first of the anterior-lobe pituitary hormones to be purified to the point of crystallization. This hormone is antigonadogenic in that it suppresses the production of follicle-stimulating hormone, it stimulates the mammary gland, which has previously been prepared by estrogen and progesterone to lactate, and, last, it has been shown by Segaloff et al. and also by Fried and Rakoff to exert a luteotrophic effect on the corpus luteum in the human being. These latter workers found that, by giving a combination of 2,000 I.U. of chorionic gonadotrophin plus 200 I.U. of luteotrophic hormone every other day during the postovulatory phase of the cycle, they were able to prolong the function of the corpus luteum. The endometria in these cases were changed from the mixed (estrogenic-progesteronic) type or the secretory type with a glyco-penia, to a normal secretory endometrium containing an adequate amount of glycogen. It is believed that this hormone either is a synergist or is identical with the luteotrophic hormone. In the above series the luteotrophic effect was obtained with much smaller doses of the chorionic gonadotrophin than those required in the series reported by Brown and Bradbury, and also there were very few adverse reactions. This combination should be valuable for clinical use in patients with menstrual dysfunction, sterility, and threatened abortion due to abnormalities of corpus luteum function.

In 1942 Hall reported on the use of prolactin alone in 34 cases of functional uterine bleeding. In 33 of the cases, bleeding was controlled with doses ranging from 300 to 2,400 I.U. given in 3 to 24 doses. Goldzieher reported good results with prolactin in a series of 98 women suffering from functional uterine bleeding.

The antihormone problem in the use of all gonadotrophins has been reviewed by Leathem. Until these products can be obtained commercially in purer forms, the adverse reactions to their protein fractions will continue to limit their effective use.

The recent work on ACTH and cortisone in anovulatory cases is discussed under Amenorrhea.

6. CURETTAGE.—Curettage, repeated as needed, is a helpful therapeutic and diagnostic aid. There is evidence, as mentioned, that the dilatation of the cervix is helpful in causing ovulation.

7. RADIATION.—The cases treated by radiation are divided into two main groups: (a) women past the childbearing period, in whom the purpose is to stop menstruation entirely, and (b) women in the childbearing age or young girls, in whom the purpose is to regulate the menstruation. In the latter group it is well to try endocrine treatment first before resorting to radiation, as the menses are occasionally stopped permanently even by small doses of radiation.

Method.—Pemberton, in a series of 131 cases, 45 per cent under twenty years of age and the rest under forty years, obtained 78 per cent of cures using radium in doses of 200 to 500 mg. hr., most of the dosages being under 400 mg. hr. Keene and Payne secured excellent results, using dosages of 200 mg. hr. if under twenty years, 400 mg. hr. from twenty to thirty years, and 300 mg. hr. from thirty to forty years.

X-ray of the ovaries, and in some cases the pituitary, thyroid, and spleen, has been reported by a number of workers. Drips claims cures in 3 out of 4; Mazer, 35 of 44; Molinari and Vierheller, 21 of 46; Kaplan, excellent results.

Radiation of an endocrine gland of such vital importance to the whole body as the anterior lobe of the pituitary has always seemed to us a rather risky method of treatment. Hence we feel that x-ray of the pituitary should be reserved for cases which do not respond to other forms of therapy.

8. OPERATION.—In young women with bleeding severe enough to damage their health, hysterectomy is sometimes necessary. Repeated curettements, however, plus endocrine therapy should be used before resorting to this radical procedure.

Childbearing Period (Twenty to Forty-Five)

In this age period bleeding is caused by conditions associated with pregnancy, inflammations in the pelvis, myomas, ovarian cysts, endocrine disturbances, blood dyscrasias, and pelvic malignancies. The relative frequency of these conditions in the childbearing period is about in the order here mentioned.

Willard Allen states: "During the active reproductive years between the ages of 20 and 40, it is always dangerous to assume that any derangement of menstrual pattern, or any abnormal bleeding, for that matter, is due to ovarian dysfunction, especially if it occurs in a person who has been having normal menstrual periods. Abnormal bleeding under such circumstances is more likely due to abortion, ectopic pregnancy, or tumors than to ovarian dysfunction, and the physician must be very wary or he will make truly serious mistakes in diagnosis and treatment. Every gynecologist sees patients who have received hormonal therapy for amenorrhea due to pregnancy and for bleeding due to cancer of the cervix. Such mistakes are not ordinarily due to ignorance; they are usually due to carelessness. In the premenopausal period the problems become even more treacherous because then abnormal bleeding becomes common, and most of it is not due to tumors. Yet failure to recognize the true cause of the bleeding may cost a patient her life."

Pregnancy complications causing bleeding can all usually be determined by the history and examination. If there is still doubt, an Aschheim-Zondek or Frog test will ordinarily settle that point. Inflammatory lesions and the larger myomas and ovarian tumors are evident from the history and pelvic examination findings. In patients approaching the age of forty, carcinoma of the uterus must always be considered, and if the bleeding does not respond promptly to treatment, there should be *no delay* in doing a therapeutic and diagnostic curettage.

In this period when the normal endocrine cycles have been fully established, the endocrine deviations are not so frequent as in the susceptible developmental period. Bleeding in the childbearing age is more likely to be due to some definite lesion in the genital tract or in some other system of the body. However, with the exclusion of lesions, including pregnancy complications, endocrine disturbance must be considered, and even with a lesion there may be associated endocrine factors. Consequently, this element must be kept in mind in all cases in which there is no other definite and sufficient cause for the bleeding. In the endocrine cases, a careful history will often show endocrine disturbances in the developmental period.

An endocrine condition causing undue prolongation of the period and profuse bleeding was described by Robert Meyer. The pathology found in the endometrium is an irregular shedding of the endometrium due to a prolongation of progesterone activity. The lesions have been reproduced in the

human being by Holstrom and McLennan and also by Masters and Magallon, by administration of progesterone. According to McKelvey, this lesion is not uncommon between the ages of thirty and forty years. The current concepts of irregular endometrial shedding has been reviewed recently by McLennan.

Clinically the periods are fairly regular, but the bleeding is prolonged to ten or twelve days and it may be very profuse, causing anemia. A curettage done on the fifth to eighth day of the bleeding, instead of showing the usual picture of a re-epithelialized endometrium, shows no surface epithelium. There are islands of endometrium present containing collapsed secretory glands with shrunken stroma and an abnormal number of spiral arterioles. Occasional islands of pseudodecidual cells may be present in the region of the blood vessels. The vessels themselves are thick walled and have open lumina which suggest that they have been retained in the functional layer from previous periods.

McKelvey found a persistence of pregnanediol secretion after the onset of bleeding in all but one of a group of such cases studied.

In regard to treatment, though no specific therapy is available, about one-half of the cases respond to curettage, and for those who do not, unless the bleeding is severe, symptomatic treatment with ergot and iron will usually tide them over until spontaneous cure occurs. Masters suggested progesterone therapy as used in anovulatory bleeding. In patients near the menopause, radiation may be indicated, and in younger patients with severe bleeding repeated curettages or even hysterectomy may be required.

The treatment-investigation program for the handling of bleeding patients in the childbearing period is much the same as that for the developmental period, with certain obvious variations. Curettage may be employed more promptly for bleeding which tends to persist, taking care, however, not to curette for the irregular bleeding of tubal pregnancy and not to be deceived by the made-up story of the woman seeking a curettage for the purpose of abortion.

Involution Period (Forty-Five to Sixty)

In the bleeding cases of this age group, pelvic malignancies come forward to the place of first importance. The malignancy may be in the form of carcinoma of the uterus or the ovaries. In regard to the uterus, carcinoma of the cervix is more frequent in the decade forty to fifty and carcinoma of the corpus in the decade fifty to sixty.

In this period of declining endocrine function, endocrine disturbances again become rather frequent, but serious ones leading to structural change are much less frequent than in the developmental period. Though granulosa-cell tumors causing bleeding occasionally occur, most of the endocrine disturbances of this period are the minor nervous and circulatory discomforts constituting the common ''menopause symptoms,'' which will be considered in Chapter 15.

In the treatment of bleeding in the period of involution, curettage of the endometrium and conization of the cervix for chronic cervicitis are to be carried out promptly on account of the danger of carcinoma in those locations.

If the microscopic examination of the curettings shows no malignancy, but only hyperplasia of the endometrium, the subsequent treatment differs somewhat according to the age of the patient. If still in the early forties with fairly regular menstruation, showing that ovulation is still going on, it is well to follow the curettage with hemostatic and endocrine treatment to control the bleeding tendency as in the childbearing period, so as to preserve the ovarian endocrine influence. If the patient is approaching the age of fifty, irradiation treatment (by radium or x-ray) should be given to stop the undue endometrial activity, as the persistence of it at that age may eventuate in endometrial carcinoma. Every patient receiving irradiation therapy should have a diagnostic curettage to rule out malignancy. The use of very large doses of estrogenic substances for the treatment of menopausal symptoms should be avoided after forty years of age.

Senile Period (Beyond Sixty)

Beyond sixty years of age, bleeding has about the same significance as it does in the latter part of the involution period. It is usually due to carcinoma of the endometrium or of the cervix uteri or of the ovaries. If no malignancy is found, the most probable cause is granulosa-cell tumor of the ovary. The bleeding here referred to is, of course, bleeding from the uterus. There may be some bloody vaginal discharge due to atrophic vaginitis or other simple inflammatory trouble, but that is easily recognized on the vaginal examination.

IRREGULAR MENSTRUATION

The menstrual flow may come too soon, the interval being only ten days or two weeks. Again the flow may not come soon enough, running overtime from one to two weeks. It is sometimes difficult to determine positively whether the irregular flow complained of is really menstruation or simply a bloody discharge from some disease of the vagina or uterus. Unless the bleeding resembles closely the menstrual flow in character and onset and duration, it should be regarded as a pathologic discharge, and an examination should be made to determine its cause, that proper treatment may be instituted.

PRECOCIOUS MENSTRUATION

Precocious menstruation is the appearance of menstruation at an early age. For genuine menstruation to take place, there must be considerable development of the genital organs, and this very rarely occurs before the age of ten, except in a patient with granulosa-cell tumor. A description of the clinical characteristics of these tumors with illustrative cases will be found in Chapter 11. Novak describes a constitutional type of precocious menstruation (see Chapter 1).

Great care is necessary, however, in establishing the fact of precocious menstruation in a given case. Every stain of blood does not mean menstruation. The blood may come from some inflamed or irritated area or ulcer, or growth on the vulva or in the vagina, uterus, rectum, or bladder. In infants a slight bloody uterine discharge occurs not infrequently within the first few days after birth, due to the withdrawal of the maternal estrin.

VICARIOUS MENSTRUATION

Vicarious menstruation is the discharge of blood from other parts of the body at the menstrual time. The uterine discharge may or may not be wholly or partially suppressed. The bleeding usually takes place from the nose or from some open sore, though it may come from almost any mucous surface, such as the lungs or stomach, or bladder, or rectum. Much more rarely some area of the cutaneous surface is affected, the axilla and the groin being the most frequent. At the affected site there appears an ecchymosis and later a distinct flow of bloody serum. The vicarious flow is likely to be irregular, appearing only at some menstrual periods. Allied closely to this is the monthly discharge of milk from the breasts sometimes observed.

Vicarious menstruation in any form is rare. Goffe records a very interesting case in which the vicarious discharge came alternately from the nose and the axilla and seemed to be associated with periods of ungratified sexual desire. Vicarious menstruation is found principally in nervous women in whom there is imperfect development of the uterus or imperfect performance of its functions. The treatment consists in the correction of any pelvic disease present and endocrine treatment to regulate ovarian function.

Some of these cases of vicarious menstruation are probably due to metastatic bits of endometrial tissue which are transplants from a pelvic endometriosis. Dr. A. P. Rubino in a personal communication described a patient under his care who bled rather profusely from one ear during periods of amenorrhea but when the normal menses occurred there was no aural bleeding. The periods of aural bleeding were accompanied by severe headache and mental confusion. On thyroid therapy the periods became regular and the periodic aural bleeding ceased.

INTRACYCLIC BLEEDING

Intracyclic bleeding is bleeding at the ovulation time. It was designated in the German literature as ''Mittelschmerz.'' It is of little significance unless it is accompanied by pain or unless the bleeding is profuse or prolonged. If it is annoying, methyl testosterone, 5 to 10 mg. orally, given daily from a few days before ovulation to a few days after ovulation will usually correct the condition. Since the bleeding is thought to be due to an excessive drop in the estrogen level in the blood at ovulation, administration of stilbestrol 0.5 mg. during the same period is also effective.

ABSENCE OF MENSTRUATION (AMENORRHEA)

Amenorrhea is the absence of menstruation for one or more periods between puberty and menopause. This definition includes the absence of the menses during pregnancy and lactation. This is known as ''physiologic amenorrhea.''

Pregnancy must always be taken into consideration in a case of amenorrhea, and before the amenorrhea is attributed to any other cause, pregnancy must be excluded—by the circumstances of the case, by questioning the patient, or by an examination.

Amenorrhea from other causes is found principally in girls and young women in whom the function of menstruation has not yet been completely established. The age of puberty, i.e., the beginning of menstruation, varies within normal limits considerably. Girls begin to menstruate, as a rule, at the age of twelve or thirteen or fourteen. The beginning of menstruation may be postponed until the age of sixteen or seventeen without disturbance. Usually, however, after the age of sixteen, and often before that, if the menstrual flow does not appear, there are disturbances that indicate some departure from normal health, and the patient may be said to have amenorrhea.

Amenorrhea is not a disease, but only a symptom. It may be an indication of any one of several entirely distinct conditions, just as a cough may be an indication of laryngitis or bronchitis, or pneumonia or tuberculosis. When a patient comes complaining that she does not menstruate, the first thing to do is to determine **why** she does not menstruate, i.e., what disease or condition lies back of this symptom.

In practice it is convenient, for purposes of diagnosis and treatment, to divide the cases of amenorrhea into two classes: one class (A) including those patients who have never menstruated, and the other class (B) including those who have.

A. WHEN THE PATIENT HAS NEVER MENSTRUATED

A mother brings her daughter, aged fifteen or sixteen or perhaps eighteen, to you, stating that the girl has never become unwell. The mother is anxious to know why the girl does not menstruate and, of course, what should be done for her.

There is a tendency on the part of physicians generally to treat this situation lightly and assure the mother that it is of no importance. The error of this advice is appreciated when, ten years later, the patient returns to know why she is unable to become pregnant and examination shows a very small, undeveloped uterus. If an investigation had been made when the mother first brought the girl to the doctor, the underlying cause of the amenorrhea might have been located and the uterus developed by proper treatment. After a uterus has remained small long past the normal time for development, the chance for improvement becomes much reduced.

When the patient has never menstruated, the absence of menstruation may be due to: (1) Some malformation, such as imperforate hymen or atresia of the vagina or imperfect development of the vagina, uterus, or ovaries. (2) General diseases or disturbances of nutrition. (3) Endocrine disturbances including tumors or other disturbances in the ovaries or other endocrine glands.

1. Malformation

Because of the possibility of there being some serious defect in the developmental processes, examination of the pelvic structures is indicated early in the investigation.

Obstruction in the genital canal gives rise to no symptoms until puberty is reached. At the age of thirteen or fourteen or later the patient begins to feel ill each month. At intervals of about four weeks she notices marked lassi-

tude and loss of appetite, feels somewhat feverish and out of sorts, has pain in various parts of the body, more particularly in the back and lower abdomen. She complains just as a woman does when she is about to menstruate. Her mother thinks menstruation is coming, but no flow appears. After a few days the pain and other disturbing symptoms subside and she feels fairly well until the next month. After several months the pain and accompanying disturbances last longer—in fact, may become almost continuous—and the patient's general health begins to suffer. A swelling may appear in the lower abdomen or at the vaginal entrance.

Such a history makes a local examination imperative. In the local examination, if the condition be imperforate hymen, the vaginal entrance is found closed. There may be a bulging of the hymen due to the pressure of menstrual blood behind it. If the atresia is situated high in the vagina, the vaginal entrance is found open, but after the examining finger has been introduced for a short distance it meets an obstruction, consisting of a wall of tissue blocking the vagina. If there is a collection of menstrual blood behind the obstruction, fluctuation may be obtained. Digital examination by the rectum will give additional information as to the location and length of the vaginal atresia and as to the amount of menstrual fluid collected behind it. In long-standing cases the vagina and uterus and even the fallopian tubes may be distended with blood.

In cases of atresia of the vagina there are likely to be other malformations higher, and sometimes the uterus is entirely absent. If the patient is past the age of puberty and no collection of blood is found above the vaginal atresia, the strong probability is that the uterus and appendages are either absent or so poorly developed that menstruation would be impossible even though the vaginal obstruction were removed. Careful examination should be made to determine certainly whether or not the uterus is present. In any case of genital malformation it is very important to get intravenous pyelograms, for, as noted in Chapter 12, malformations of the urinary tract frequently accompany those of the genital tract.

In opening into the blood collection in a case of imperforate hymen, careful asepsis must be maintained, for the old blood is a culture medium for the rapid growth of any bacteria introduced, and if the collection extends to the uterus and tubes, serious sepsis may result. The remedying of any defect greater than imperforate hymen requires special surgical work, the details of which are given in the authors' *Operative Gynecology*. Congenital agenesis of the ovaries has been discussed in Chapter 12.

2. General Diseases

General diseases may cause amenorrhea by depressing the functional activity of the endocrine system or by affecting the general nutrition through vitamin deficiency or damage to the blood or organs, or by a combination of these effects. Chronic diseases, such as tuberculosis, malaria, or syphilis, which tend in one way or another to depress the vitality of the patient, may cause amenorrhea. Hesseltine, in a discussion of Randall's paper, found that in 62 patients with pulmonary tuberculosis amenorrhea was present in 27 per cent of those between the ages of fourteen and nineteen, and 72 per cent of

those between the ages of twenty and twenty-five, emphasizing the importance of ruling this disease out before starting therapy. Acute diseases, especially mumps, occasionally cause enough ovarian damage to produce amenorrhea.

3. Endocrine Dysfunction

If the amenorrhea cannot be accounted for by any of the above conditions, an endocrine investigation is indicated.

The general physician faced with the problem of outlining endocrine therapy for a case of amenorrhea naturally feels a certain inadequacy because of his inability to obtain the various hormone tests required in certain cases. This, however, need not deter him in his efforts, for much can be done in many cases with the ordinary diagnostic and treatment procedures. The intelligent use of the means at hand will enable him to treat successfully the cases which can be thus handled and to differentiate the more serious cases which require the extensive investigations and radical treatment measures available in the large medical centers.

Since the investigation and treatment of endocrine cases are the same whether the case is one of primary or secondary amenorrhea, these will be taken up later under secondary amenorrhea.

B. WHEN THE PATIENT HAS MENSTRUATED

When the patient has menstruated and later ceases, the amenorrhea may be due to (1) physiologic amenorrhea, (2) some general condition, (3) pelvic lesions or treatment, or (4) endocrine dysfunction.

1. Physiologic Amenorrhea

Normal Pregnancy.—If the patient has previously been regular in menstruation, is in good health, and has had an opportunity to become pregnant, the natural supposition is that she is pregnant, and until it is proved that she is not, nothing should be done that could in any way interfere with pregnancy.

The patient may assert positively that she is not pregnant, may even deny any possibility of pregnancy, but when after examination there is any suspicion in your mind, postpone all local treatment until after the next menstrual flow. If you doubt the patient's honesty—that is, if you think she may return and tell you that she menstruated when in fact she did not—tell her that she must come during the flow, that you may determine the character of the flow. In this way you can establish certainly whether or not she really menstruates.

In this matter of the question of pregnancy, it requires considerable judgment and tact, on the one hand, to detect the cases of pregnancy and, on the other hand, to avoid wounding the feelings of innocent persons by ill-advised questions. Concerning the question of pregnancy, the cases may be divided into three classes. In the first class come the girls and unmarried women in whom, from the character of the trouble or from the known character of the patient and the examination findings, the possibility of pregnancy may be at once eliminated. These correspond very closely with the patients who have never menstruated and require the same treatment.

In the second class come the married women. If the diagnosis is still doubtful after examination, the patient is told that it is too early yet to be certain about it, and she is directed to come again after a month or six weeks. If the patient is anxious to know at once, then a pregnancy test should be done.

In the third class come the girls and unmarried women about whom you know but little—they may be all right or they may be all wrong; you simply do not know and hence must be cautious. In this class come also widows, divorced persons, women living apart from their husbands—all of whom, if pregnant, might wish to conceal the fact. Some of these patients are perfectly truthful with the physician, telling him their fears or leaving a clear opening for the asking of questions that would bring out the information. In other cases the patient gives the whole history of her case without any intimation of a misstep. Occasionally the patient tries deliberately to deceive the physician, hoping that in his examination or treatment something may be done that will bring about an abortion.

In such uncertain cases it is usually best for the physician to keep his thoughts to himself, and not to intimate any suspicion of pregnancy until some good evidence of it is found. Do not depend too much upon the history the patient gives. Just keep in mind that it may be all truth and it may be all falsehood. If after examination there is still doubt, a pregnancy test will ordinarily be decisive in the matter. If this is negative the prostigmine test should be tried. This consists in giving 1 c.c. of 1:4,000 prostigmine by hypodermic daily for three days. If the patient is not pregnant and has no marked endocrine disturbance, she will menstruate shortly after the last dose. To date, this procedure has never been known to cause abortion.

In the exceptional cases where it is thought best not to suggest the possibility of pregnancy at the time of local examination, a specimen of urine may be requested on general principles, and the pregnancy test made. From three to four ounces of morning urine are satisfactory for the laboratory work. In this way the physician protects himself and at the same time gives the patient good treatment. If it turns out that no pregnancy is present, the patient need never know that pregnancy was suspected. On the other hand, if it turns out that pregnancy is present, nothing has been done that could possibly interfere with it.

Extrauterine Pregnancy.—The evidences of tubal pregnancy have already been given in Chapter 10. In the case of a doubtful pelvic mass the pregnancy test may help in differentiation.

Lactation.—As a rule, a woman does not menstruate while nursing a baby. There are, however, many exceptions to this rule, especially after the first six months. Quite frequently a patient, while nursing her child, will begin to menstruate within five or six months after labor and occasionally within two or three months. This happens most frequently in those cases in which the mother has only enough milk to partly nourish the baby.

Beginning Menopause.—The age at which the menopause begins varies much in different persons. The average age is about forty-five, but it often begins somewhat earlier, in exceptional cases before forty. If the patient is past forty and the menstrual flow has been getting gradually less for several months, the menopause is probably beginning. There are two separate phenomena that usually accompany the climacteric and that may aid in the diagnosis—the "hot flashes" with some irritability and other evidences of nervousness, and the tendency to increase in the subcutaneous fat deposit. Neither one of these is pathognomonic, but both of them occurring in a patient past forty, with menstruation gradually diminishing, make the diagnosis of the climacteric fairly certain.

2. General Conditions

Changes in Routine or in Climate.—A long journey (particularly on the ocean), change of residence from country to city, or vice versa, extraordinary grief, joy, anxiety, or exciting work, study (as in preparing for examinations), taking up a new occupation, financial troubles, love affairs, and difficulties in home life, any of these may cause an expected menstruation to be missed.

When the amenorrhea is apparently due to these causes, it is usually a sign of slight endocrine deficiency and, as a rule, is due to a mild hypothyroidism.

Nutritional Disturbances.—The importance of nutrition in amenorrhea has long been recognized. During wars (Whitacre and Barrera) and in other situations where starvation conditions exist, amenorrhea is common. Allen and Heckel have shown that, in animals fed on a diet low in calories but adequate in other dietary elements, regressive changes occur in the pituitary and secondarily in the ovary which may become irreversible. Our recent knowledge of the relationship of vitamins and other accessory food elements to endocrine function has emphasized the importance of a diet adequate in vitamins, minerals, trace elements, and calories.

A simple case of undernutrition can be corrected by a high-calorie diet plus the supplements mentioned above, but in cases of severe malnutrition, emotional disturbances, and sudden shocks, special measures are required. Recent work indicates that the effect may be mediated through a nerve center in the hypothalamus which influences the secretion of the pituitary hormones. The condition of anorexia nervosa is one in which the most extreme degree of inanition is found, and in these cases the quantity and quality of the food have been restricted to such a degree that re-education of the gastrointestinal tract is necessary. Randall reported 15 cases associated with amenorrhea, and he found that amenorrhea was present in 50 per cent of his cases of anorexia nervosa. Berkman recommends starting these patients on a diet of 300 calories more than she has been taking, then increasing the caloric content by 300 calories every three to five days until a daily total of 3,400 to 3,600 calories is reached. Vitamins, minerals, trace elements, and iron are added to the diet. The basal metabolism, which may be as low as -35, will usually come up to normal on the diet without the addition of thyroid.

Thayer found that in difficult cases insulin before the meals helped in the assimilation of food, and Liegner, in two cases of long-standing amenorrhea in undernourished women, initiated menstruation by giving insulin, intravenous glucose, and high carbohydrate feeding, until normal weight was reached.

In overweight girls with endocrine disturbances and amenorrhea, consistent reduction of weight on a low-calorie diet containing adequate vitamins and other necessary elements will usually result in normal endocrine function. In these cases the thyroid function is frequently low and the addition of thyroid will speed up the return to normal.

Simple anemia is frequently a factor in the causation of amenorrhea and, if present, should be corrected by *iron* administration, preferably a product containing ferrous sulfate, trace of copper, and vitamin B complex.

Acute and Chronic Diseases.—These have been discussed under primary amenorrhea.

3. Lesions in Pelvis or Elsewhere

Lesions affecting the pelvic organs or distant organs concerned with pelvic function may cause amenorrhea.

Distant Organs.—Tumors or dysfunction of the pituitary, adrenal, or pineal glands may, among other things, cause amenorrhea, but usually this symptom is a minor problem, being overshadowed by numerous other striking signs and symptoms. The differential diagnosis of these conditions is discussed later under Endocrine Dysfunction, for the symptoms that they produce are due to altered endocrine balance.

Local lesions which may cause amenorrhea are those affecting the ovaries and those affecting the uterus.

Ovarian Disease.—With most ovarian diseases extensive enough to cause amenorrhea, the ovarian disease overshadows the amenorrhea in importance. There is, however, one exception, namely, thickening of the capsule of the ovaries. This may be sufficient to prevent ovulation and menstruation without otherwise troubling the patient. Operation by stripping off portions of the thickened capsule of each ovary or the wedge operation recommended by Stein and Leventhal, as mentioned in Chapter 12, may be done. Occasionally secondary involvement after mumps may interfere enough in function to cause a cessation of menses. Agenesis of the ovaries was mentioned under Primary Amenorrhea. Tumors of the ovaries most commonly accompanied by amenorrhea are adrenal rests and arrhenoblastoma.

A previous history of pelvic operative work followed by amenorrhea when the uterus is still present indicates either bilateral oophorectomy or preservation of an inadequate amount of ovarian tissue to permit normal function. Exposure to irradiation either by x-ray, radium, or radioactive materials may cause amenorrhea; hence great care should be exercised by women working in occupations dealing with these materials to be sure that they are properly screened.

Uterine Conditions.—Developmental anomalies of the uterus and genital tract which would preclude menstruation have been mentioned and of course absence of the uterus is one of these.

Hypoplasia of the uterus in which the uterus is very much smaller than normal and the endometrium is inadequately developed, may be due to failure of full primary development, as in an infantile uterus, or development may have reached the adult stage but endocrine stimulation has either been inadequate or it has been withdrawn after full development and function. In the first instance the characteristic finding is a large cervix and a small fundus, the ratio being 4:3 instead of the normal 3:4 ratio found in the adult uterus; in the second type the ratio between the cervix and the fundus is normal but the uterus is very small, similar to the type found after the menopause. The differential diagnosis and treatment of this type of case will be discussed under Endocrine Dysfunction. Such a uterus, as seen by peritoneoscope, is shown in Fig. 972, from an article by Wilkins and Fleischmann.

4. Endocrine Dysfunction

Exclusive of congenital malformations in which menstruation is not possible, amenorrhea is caused by direct or indirect disturbance of normal endocrine function. The first step, when confronted by a patient with a chief complaint of amenorrhea, is to attempt to determine, if possible, the etiological factors involved. By means of an accurate history, physical examination, and

available clinical tests which can be done in the office, most of these cases can be diagnosed with a degree of accuracy which will permit the physician to determine whether the patient has one of the unusual conditions requiring special tests obtainable only in large medical centers or whether she has a good chance of responding to endocrine therapy. In some cases a trial of therapy for several months may be necessary as an aid in the differential diagnosis.

Special tests which enable one to differentiate more accurately the etiology of the amenorrhea, such as levels of the various hormones in the blood and urine, are usually available only in large centers and hence they cannot be used, as a rule, by the man in general practice. The interpretation of these tests will be discussed briefly under conditions where they are helpful in establishing a diagnosis.
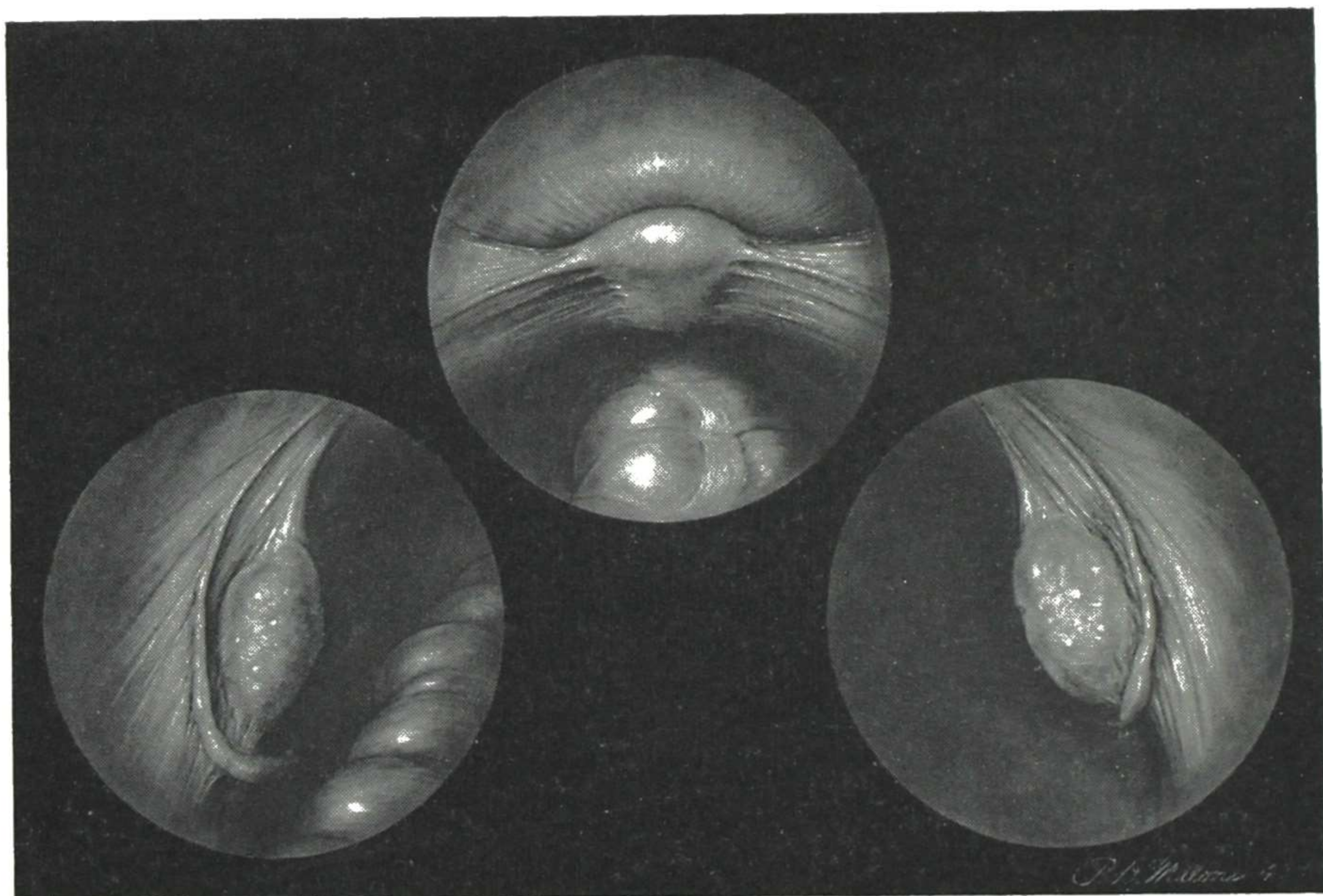
Fig. 972.—Peritoneoscopic view showing fairly well-developed ovaries with follicles.   (From Wilkins and Fleischmann: J. Clin. Endocrinol., July, 1944.)

1. In the history, points of importance are: previous diseases, such as mumps, tuberculosis, diabetes, blood dyscrasias; pelvic operations; radiation exposure; psychic shocks or disturbances; menses, date of onset and regularity in cases of secondary amenorrhea.

In the physical examination, points indicative of endocrine dysfunction are general build. Pertinent measurements are relationship of height to span and distance from the floor to the symphysis pubis and from the latter to the crown of the head. The importance of these measurements is discussed in Chapter 11. The fat distribution, development of the secondary sex characteristics, and the hair distribution may give a suggestion as to the gland involved. Marked hypertrichosis is found in a number of conditions and its degree and distribution may serve as an aid in the differential diagnosis between such conditions as pituitary tumors, adrenal tumors, of the ovary,

adrenogenital syndrome, and pineal tumors. Bissell and Williams give an excellent classification of hirsutism which can be used in cataloging patients. Cantillo and Calvo emphasize the importance of the adrenal in 100 cases of hypertrichosis. De Paiva reports a case of primary amenorrhea caused by an adrenal tumor in which menarche and pregnancy followed the removal of the tumor.

Another condition which will cause primary amenorrhea is the Laurence-Moon-Biedl syndrome. This is characterized by familial hypogonadism, mental retardation, atypical retinitis pigmentosa, obesity, skeletal deformities, especially dwarfism and polydactylism.

An accurate differential diagnosis of cases of the above types requires careful study in a hospital where special tests are available, but the general physician should be able to recognize that there is a diagnostic problem involved so that he can advise the patient to seek expert consultation.

On vaginal examination developmental defects are ruled out. Vulvar development and hair distribution are noted. Size of the vagina and condition of the mucosa, size and direction of the cervix, and its relative size in comparison with the fundus are important. The size and position of the uterus as an aid in diagnosis have been discussed above under Uterine conditions. The cavity of the uterus should be measured by means of a graduated sound. This confirms the size of the uterus, and subsequent soundings during treatment will serve as an index for the results with treatment.

Enlargement of the ovaries, taken together with other signs and symptoms, may point to an ovarian tumor such as an arrhenoblastoma or adrenal rest as the cause of the amenorrhea.

2. Some of the general tests are basal metabolic rate and, if indicated, x-ray of the sella turcica, visual fields, and sugar tolerance tests. These latter are helpful in cases of suspected pituitary tumor. For an excellent review of the practical aspects of insufficiency of the anterior pituitary gland, the reader is referred to a recent article by Perkins and Rynearson. Sosman has reviewed the salient features found in pituitary basophilism.

The basal metabolism test should be taken only as a general guide to whether the patient needs thyroid, and in general again we usually give a grain of desiccated thyroid for each −10. Means, in a Presidential Address at the 1949 meeting of the American Goiter Association, gave a paper entitled ''Confessions of an Elderly Thyroidologist,'' in which he stated: ''The symptoms are a better guide to treatment than the BMR. Now we know that the objective should be to rid the patient of symptoms with the smallest ration of thyroid that will do it.'' In the doubtful case the blood cholesterol level and the uptake of radioactive iodine may prove valuable diagnostic aids.

3. The next step in the investigation is to determine whether the patient is ovulating; for if she is, the problem is merely one of reinforcing the patient's hormone levels by cyclic estrogen and progesterone therapy. In most cases of amenorrhea, ovulation does not occur and this may be due to inadequate secretion of pituitary gonadotrophins or inability of the ovary to respond to the normal stimulation of the pituitary gonadotrophins.

An endometrial biopsy will not only give information as to whether ovulation has occurred, but it will also indicate the amount of estrogenic stimula-

tion present. Amenorrhea can be caused by excessive estrogen stimulation, in which case a hyperplastic endometrium will usually be found. A vaginal smear, stained for glycogen by the iodine-vapor technique, will usually serve to indicate whether there is an adequate amount of endogenous estrogens and progesterone. The use of the vaginal smear and temperature chart as indications of ovulation and hormonal activity has been discussed in Chapter 11.

4. In cases showing no evidence of ovulation the next step is to determine whether this is due to failure of the pituitary to secrete the gonadotrophic hormones or inability of the ovary to respond to the gonadotrophic stimulation.

Ovarian failure occurs physiologically in the menopause when the ovary no longer secretes, but the endometrium, though atrophied, retains the ability to respond when exogenous estrogens are given. With withdrawal of the blood estrogen the inhibition on the basophilic cycle in the anterior lobe of the pituitary is absent; hence the basophilic cells collect and become filled with vacuoles and are designated as castration cells. Since these cells continue to secrete the gonadotrophic hormone, excessive amounts are found in the urine and this finding is diagnostic of primary ovarian failure. If a consistent increase in the urinary level of follicle-stimulating hormone is found, the diagnosis of primary ovarian failure is conclusive.

Where this test is not available, a clinical test was suggested by Hamblen as follows:

A dose of pregnant mares' serum is administered, using Anteron (200 units) or Gonadogen (20 to 40 units). This is given intramuscularly, after previous allergic study to rule out serum sensitivity. The dose is repeated daily for three or four weeks, during which time careful clinical observations are made, including a bimanual examination twice a week to evaluate alterations in the genital tract. In the pelvic examinations, special attention should be directed to the ovaries, and if cystic change occurs, a rest period is allowed. Measurement of the uterine canal with the occasional endometrial biopsy will give accurate information on uterine and endometrial growth. The daily dosage should not be continued longer than three or four weeks at a time, because of the possibility of the ovaries becoming refractory due to the antihormones or to lowered receptivity. If there is no evidence of ovarian response after several series of such medication, the probability is that the condition is one of primary ovarian failure.

In primary ovarian failure where its ability to respond is completely absent, such as the menopause or agenesis of the ovaries, hormone therapy is indicated only for relief of symptoms caused by lack of estrogens. In agenesis, treatment is used to develop the secondary sex characteristics so that the patient may appear to be normal. This is important from a psychological standpoint, and though these patients are permanently sterile they may enjoy normal married life.

In cases of secondary ovarian failure, the ovary is able to respond in part to the pituitary stimulation by secreting estrogens, but ovulation does not occur. This is seen in the Stein-Leventhal syndrome where the cortex of the ovary is markedly thickened and in cases where excessive amounts of estrogen are secreted, increasing the inhibition of the pituitary secretion. In these latter cases a hyperplasia of the endometrium is usually present, and though bleeding does occur the endometrium shows no evidence of a preceding ovula-

tion. The cases of secondary ovarian failure are due to a disturbance in the pituitary-gonadal balance, and such cases are the ones which respond best to therapy.

With secondary ovarian failure, if there is an inadequate secretion of both estrogens and progesterone, the uterus will be hypoplastic, and in cases where there is excessive estrogen secretion the uterus may be of normal size or it may be somewhat larger than normal.

If the amenorrhea is due to pituitary failure, the diagnostic point is a marked decrease or absence of follicle-stimulating hormone in the urine.

It must be realized that a clear-cut classification of cases into these various categories is not always possible, and a trial of therapy will sometimes not only enable the patient to menstruate but it may give a lead in helping to classify her type of amenorrhea.

5. The next step in cases of amenorrhea due to endocrine disturbances is planning treatment, and this varies with the type of amenorrhea.

a. Cases of primary ovarian failure, as mentioned above, require only symptomatic treatment as there is no known therapy that will correct agenesis of the ovary or cause an exhausted postmenopausal ovary to be rejuvenated.

b. In cases of secondary ovarian failure, without some evident lesion such as tumor of the ovary of other endocrine glands, we can divide the cases roughly into those in which there is an evidence of an insufficiency of both ovarian hormones and those in which there is an excess of estrogen and an absence of progesterone.

In the first group, where there is an insufficiency of both ovarian hormones, it is difficult to be sure whether the crucial etiologic factor is a poor response by the ovaries to adequate pituitary stimulation or inadequate gonadotrophic secretion to elicit a normal ovarian response; hence a combination of ovarian and pituitary therapy is frequently advisable. These patients may be cases of primary amenorrhea or they may have had an occasional period. They have many signs of low estrogen secretion, such as poor development of breasts, pubic and axillary hair. The build is usually indicative of late closure of the epiphysis with the measurement of the span exceeding that of the height and the measurement from the floor to the symphysis greater than that from the symphysis to the crown of the head. Pelvic examination reveals hypoplastic external genitals and small, short vagina with a poorly developed mucous membrane. The cervix is small and the uterus is hypoplastic. Measurement of the cavity should be taken if possible as this not only confirms the small size of the uterus but serves as a point for comparison when trying to estimate the effectiveness of therapy.

The therapy advocated in this type of case varies with different authorities in the field of endocrinology; some advise cyclic estrogen and progesterone, others use gonadotrophins only, and still others use x-ray therapy. All have had a certain degree of success and frequently it is necessary to combine all three. I shall try to summarize briefly a plan for treating this type of case.

First, the general nutrition should be brought up or down to normal, and general diseases such as tuberculosis and other causes for amenorrhea should

be ruled out. Next the function of the thyroid should be investigated and thyroid extract given if indicated.

Second, cyclic estrogen therapy alone or in combination with progesterone is started. Zondek used estradiol benzoate 2.5 mg. and progesterone 12.5 mg. by hypodermic, repeated in forty-eight hours, and found that this combination would usually cause the patient to bleed in a few days; however, this had to be repeated monthly. Oral therapy has been found to be just as effective and it is much more satisfactory because it is usually necessary to treat these patients over many months before their own endocrine mechanism begins to function.

Various estrogens are used for cyclic estrogen therapy and the daily dose varies: stilbestrol 0.5 to 2.0 mg., hexestrol (Harding) 9 to 48 mg. daily from the fourth to the twenty-fourth day, estrone sulfate 6.5 mg. daily from the second to the twenty-second day of cycle (Hamblen), or estrone sulfate soluble 3.0 mg. daily (Birnberg et al.). Friedberg injects 1 c.c. of a suspension containing 2.5 mg. of crystalline diethylstilbestrol dipropionate into each side of the cervix, once a month.

Progesterone when used with the estrogens is usually given daily during the last six days of the course. If given intramuscularly, the dose is 10 mg. daily for six days; if used sublingually, W. Allen advises 40 to 50 mg. daily for six days; and when given orally, Greenblatt et al. recommend 80 to 100 mg. daily for five days.

In treating this type of patient we have usually started in with oral stilbestrol if the patient can take it, working the dose up gradually to 2 mg. daily for twenty days, or from the second to the twenty-second after the cycle has been established. This has usually been continued over a period of months in cases of uterine hypoplasia until the uterus has shown some sign of enlargement. After the uterus has enlarged, sublingual progesterone 40 to 50 mg. daily is given from the twentieth to the twenty-sixth day of the cycle. When the periods of bleeding are fairly regular and the size of the uterus approaches normal, an endometrial biopsy is done to see if ovulation has occurred, and, if not, pregnant mares' serum and chorionic gonadotrophins are given in the proper relation to the cycle. Some men advise, in addition, the preparations made from the anterior lobe of the pituitary and also prolactin, which is probably identical with the luteotrophic hormone.

Hamblen advises 500 I.U. of pregnant mares' serum daily from the fifth to the fourteenth day of the cycle, followed by 500 to 1,000 I.U. of urinary gonadotrophin daily from the fourteenth to the twenty-fourth day. If bleeding occurs, the injections are stopped, but if the patient fails to respond, the daily dose of pregnant mares' serum is increased to 1,000 or 1,500 I.U. Rest periods are imperative to avoid antihormone formation. Bonime obtained good results using pregnant mares' serum. The use of a preparation containing the urinary gonadotrophins and the anterior lobe pituitary synergist (Synapoidin) has been discussed under treatment of functional bleeding.

Because of the danger of allergy and development of antihormones, as well as the inconsistency of results, many workers in this field have discontinued the use of the pituitary preparations, but the results reported by such men as Hamblen and others in some cases certainly warrants a trial of this

therapy in difficult cases. In recent years ACTH and cortisone have been tried in pituitary insufficiency; an excellent summary by Perkins and Rynearson was published in May, 1952. Davis et al. have used ACTH experimentally in twelve women with secondary amenorrhea with good results, but they warn that this is entirely experimental and in no way indicates that this substance is recommended as a proved treatment for secondary amenorrhea. At a recent meeting of the American Society for the Study of Sterility, Dr. Seegar Jones reported the use of cortisone in a selected group of refractory sterility and amenorrhea cases with good results in some cases, but she again emphasizes the dangers of therapy and need for careful observation, also the need for more extensive investigation before this therapy can be recommended for general use.

The use of low dosage x-ray to the pituitary and/or ovaries has been advocated in amenorrhea and sterility by Kaplan since 1930, but most gynecologists have hesitated to use it for several reasons. First the danger of destroying entirely the ovarian function in a patient in whom this function is already at a low ebb, and second because of the reported damaging genetic effect on future generations in the Drosophila and some animals. In a recent report Kaplan reports on the follow-up of 362 cases which were given low-dosage radiation for amenorrhea or sterility; 292 of these resumed normal menstruation and, of these, 168 became pregnant. Of 180 normal children born to these women, two have already had a normal child, showing that there was no deleterious effect on the second generation. Excellent results have also been obtained by other workers, by Mazer et al., by Drips, by Randall, by Payne, and by Israel. Collins, in 1950, in replies to a questionnaire on the subject from 410 gynecologists, found that 70 per cent of them did not use it and 43 per cent condemned its use. Of the 4,202 collected radiated cases there was only one case of known bad result, though some of the gynecologists stated that they knew of twelve cases of persistent amenorrhea and four additional bad results of undetermined nature.

The action of the x-ray is still not clear; it may affect the pituitary or it may cause absorption of persistent corpora lutea or rupture of mature follicles. Streeter, in a personal note to Kaplan, thought that the treatment killed off all the primordial follicles and that a new crop of follicles and their accessory cells developed. All those using this therapy emphasize the danger of radiating an early unsuspected pregnancy and recommend sexual abstinence for two months before and after treatment.

The technique as advised by Kaplan is as follows:

"The irradiation is carried out with the following factors: 200 kv., 0.5 mm. Cu plus 1 mm. Al filter, at 50 cm. distance through 8 by 10-10 by 15 cm. fields for the ovaries and a 6 by 8 cm. or a 5 cm. round field for the pituitary area. A dose of 50 r in air is given to each anterior ovarian field and 75 r to the anterior pituitary field for the first exposure. One week later, 75 r is given to each posterior ovarian field and 75 r to the anterior pituitary field for the second exposure. Again one week later, 50 r is given to each anterior ovarian field and 75 r to the anterior pituitary field for the third exposure. This completes the series. A fourth exposure is administered only in rare instances."

With this wealth of factual evidence this treatment certainly deserves a prominent place in our therapy of amenorrhea and sterility.

In cases of amenorrhea due to an excessive amount of estrogen in the blood causing hyperplasia of the endometrium, there are frequently long periods of amenorrhea with an occasional break-through bleeding. In these cases the endometrium is already primed with estrogen, so cyclic progesterone will usually cause a good desquamation of the endometrium and this is frequently followed by normal cyclic periods.

Before leaving this discussion of amenorrhea in which prolonged use of various hormones is sometimes indicated, reference should be made to two articles which caution us as to the dangers involved: "Untoward Effects of Endocrine Therapy" by The Council on Pharmacy and Chemistry of the American Medical Association, and "Endogenous Allergy to Steroid Hormones" by Heckel (see References).

PAINFUL MENSTRUATION (DYSMENORRHEA)

Dysmenorrhea is one of the most frequent symptoms met with in gynecology and, in some cases, it is one of the most difficult to treat. Even among the women of ancient times this complaint was common and prescriptions for relieving menstrual pain have been found in the Egyptian writings (the Ebers and Kahun papyri) as early as 2000 B.C. One such remedy consisted of a poultice containing crushed onions and pine sawdust.

Estimates as to the frequency of dysmenorrhea vary greatly. Stone estimated that 35 per cent of all women complain of some pain with the period. Among 1,400 women students at the University of California, Cunningham found that 50 per cent complained of some pain, and 35 per cent complained of severe pain.

W. B. Brown compiled statistics from 29 colleges and universities and found that of 31,309 women students 45 per cent claimed some type of pain at the period time and 14.6 per cent suffered severe pain requiring bed rest. J. O. Haman in calculating the industrial importance of dysmenorrhea figured that if 16.6 per cent of the 32 million women between the ages of 15 and 50 were laid up for two hours a period, or twenty-six hours a year, there would be 140 million hours lost annually due to dysmenorrhea. On the basis of a norm of 2,400 working hours a year per person, this loss of time represents an entire year of work by approximately 58,000 women. Not only is the actual time lost of importance, but also the many hours of inefficiency while the woman is in pain and attempting to carry on her job.

Etiology

The myogenic factors in normal and painful menstruation have been investigated by numerous workers and the method used by most of them is the intrauterine balloon. It has been demonstrated that uterine contractions in normal and dysmenorrheic women are identical until the time of menstruation. The uterus possesses an intrinsic motility and it is continually contracting and relaxing; during the first half of the cycle the contractions are of low amplitude, rather frequent, and are superimposed upon a moderate degree of uterine tonus; during the second half of the cycle the contractions assume a much higher amplitude, are less frequent, and the tonus is abolished. This latter type of contraction persists throughout the menstrual cycle.

This intrinsic pattern is not altered by resection of the presacral nerve, though in a recent study by Bickers, "Dysmenorrhea and the Pelvic Autonomic System," it was found that there was some change in the vasomotor control of the blood flow through the uterus. It has been clearly established that estrogen is responsible for the low contractions during the first half of the cycle and progesterone for the higher ones occurring during the last half.

Many conflicting findings have been reported in tests on dysmenorrheic women, but one fact which is universally accepted is that primary dysmenorrhea occurs only when ovulation has preceded menstruation and progesterone is present in the blood. In support of this is the fact that dysmenorrhea can be prevented in dysmenorrheic women by inhibiting ovulation and, again, cramps can be produced during anovulatory cycles by administration of progesterone.

The exact cause of the cramplike pain, which occurs when the muscular contraction is at its height and the intrauterine pressure exceeds the patient's blood pressure, is still a matter of some dispute. Moir believes that it is due to ischemia and hence anoxia of the muscle. Bickers agrees with this and finds in addition, that the dysmenorrheic contraction was superimposed upon a myometrium which was already in a high state of tonus, and he feels that the abnormal behavior of the muscle is due to a congenital physiologic defect in the muscle itself. Smith and Smith have shown that in the catabolic stage of the cycle the endometrium produces a menotoxin, probably a euglobin, and a lytic substance which not only cause excessive irritability of the muscle but also affect other areas of the body, causing the symptoms of menstrual molimina. In confirmation of this, Phelps found an increased oxytoxic effect on the uteri of rabbits when urine of dysmenorrheic women was injected, indicating that the general circulation of these women contained some substance causing uterine spasm.

Local conditions such as passage of clots may be a factor, for it is well known that dilatation of the cervix, or pulling the partially deflated intrauterine balloon through the cervix will reduplicate the dysmenorrheic pain. Emotional upsets will cause an increase in the amplitude of the uterine contractions, but only if the patient is in the last half of the menstrual cycle.

From a clinical standpoint it is customary to divide cases into two categories: (1) Primary dysmenorrhea. This usually starts at the menarche or shortly thereafter and is characterized by cramplike pains in the pelvic region starting a day or so before the period. The pain frequently radiates down the thighs and into the lower back. The patient usually complains of general malaise, nausea, weakness, and this is accompanied by vasomotor changes causing pallor, cold sweats, and occasionally fainting. (2) Secondary dysmenorrhea. This usually starts later in life. The type of pain and the time of its onset are not constant. The etiological factors involved in this type are usually more easily determined than they are in the primary type.

Because of the psychogenic factor it is very difficult to estimate the true effectiveness of any drug given hypodermically, as the psychic effect of a shot is difficult to discount. Even in a series of cases where the medication was given by mouth, Boynton and Winther found that the psychic element was very important. In 100 unmarried women between the ages of seventeen

and twenty-five suffering from primary dysmenorrhea, they gave 50 patients placebos and the other 50 patients estriol glycuronide tablets. Twelve per cent of the group receiving the estriol glycuronide and 8 per cent of the group receiving the placebos reported complete relief from the dysmenorrhea for a period of nine to twelve months.

Haman investigated the threshold for pain in dysmenorrheic women compared with a control group of normal women and men and found that the average pain threshold in the dysmenorrheic group was lower than that for the other groups. This lowered threshold is retained even past the menopause, suggesting an intrinsic factor that renders a dysmenorrheic woman more susceptible to pain than the nondysmenorrheic.

The question of the degree of pain a patient has, of course, depends entirely upon her interpretation of a subjective symptom, and this fact makes the investigation and evaluation of treatment very difficult.

The degrees of pain can roughly be graded as follows: (1) mild type—some pain but not enough to require medication; (2) moderate type—some medication required but not confined to bed; (3) severe type—patient forced to bed with her periods.

Therapy

Since there is no single cause for dysmenorrhea, classification for treatment is difficult; though certain types can be classified on an etiologic basis, many cannot. For convenience, the following outline is used for a discussion of therapy:

1. Primary Dysmenorrhea: Mental and physical hygiene, general measures, neurogenic and myogenic sedatives, and endocrine therapy.

2. Secondary Dysmenorrhea: Pelvic and extrapelvic lesions, mechanical causes, allergy, and disturbed water balance with sodium retention.

Primary Dysmenorrhea

The importance of **mental and physical hygiene** has long been recognized. We all know of instances where dysmenorrhea has been consciously or subconsciously used as a shield to avoid an unpleasant situation.

The importance of psychosomatics in gynecology has frequently been stressed by Cooke, who states, "Ninety-five per cent of the severity of human suffering is mental; a great deal of the symptomatology encountered in the practice of gynetics is of purely mental origin." An excellent method of diagnosing and treating functional disease is given by Lock and Sluder, and the psychosomatic aspects of dysmenorrhea are reviewed by Hunter and Rolf; the reader is referred to these articles for further details.

Because of the important part suggestion plays in the treatment of dysmenorrhea, it was logical to expect good results from hypnosis. Success with this type of therapy was reported by Dick in 1925. In 1943 Kroger and Freed, using hypnosis together with psychoanalysis and age regression, treated nine cases of severe dysmenorrhea. All of the patients had had other forms of treatment including antispasmodics, endocrines, and, in some cases, dilatation and curettage. Seven of the patients were completely cured and two were not helped.

This form of psychotherapy aids by raising the threshold for pain directly or through the elimination of the psychogenic factors causing the pain.

A typical case was one of a seventeen-year-old girl who had had extensive medical therapy and a dilatation and curettage. The pain was so severe that presacral sympathectomy had been advised and the patient had agreed to have
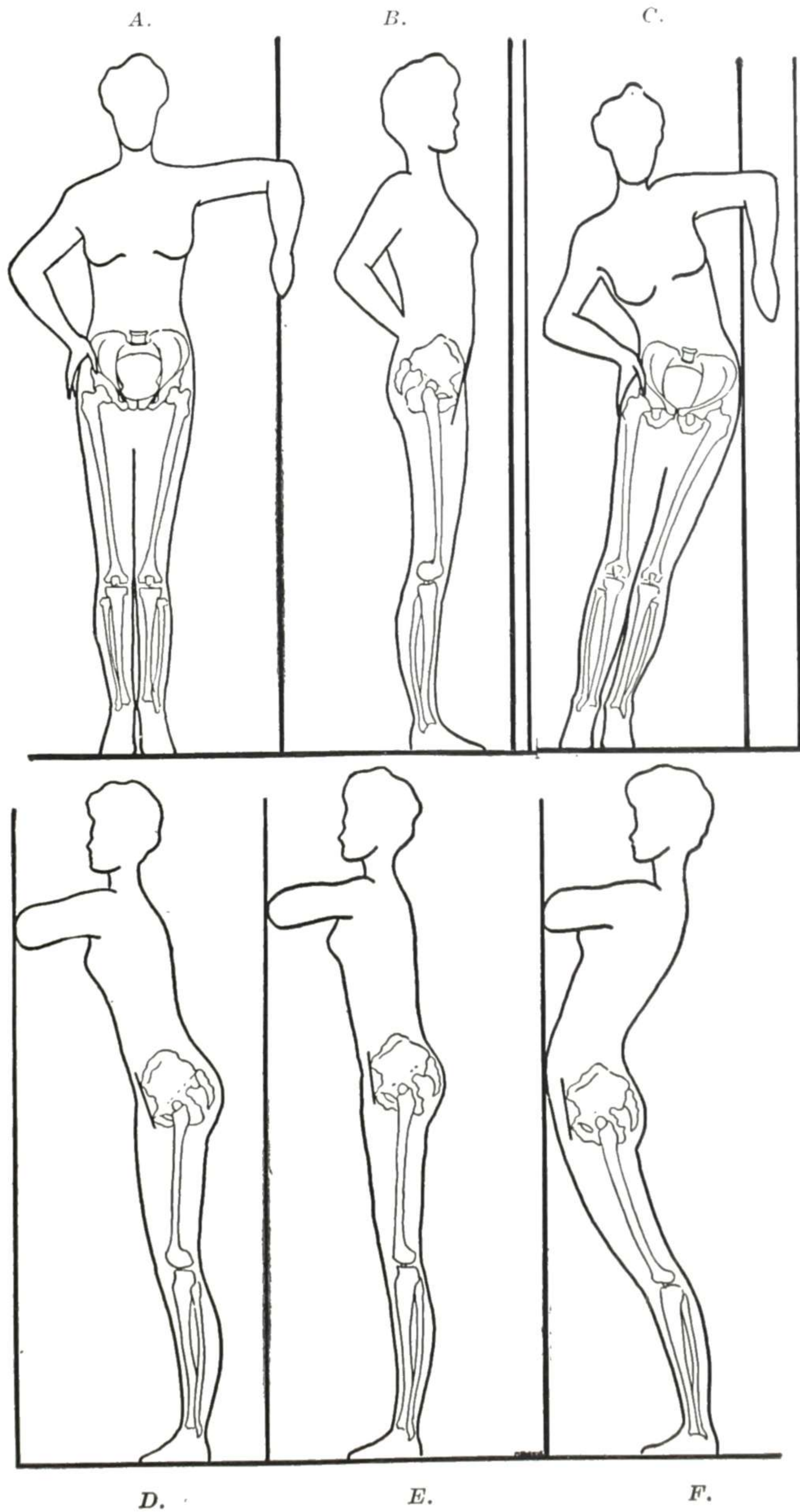
Fig. 973.—Haman exercises in dysmenorrhea. *A*, The patient stands at right angle to the wall at a distance that will enable her to rest her left elbow comfortably on the wall on a level with her shoulder. *B*, Lateral view showing hand on opposite hip. *C*, The pelvis is tilted forward and, while in this position, the patient touches the wall with her left hip, keeping the knees straight. The same procedure is carried through for the right side. *D*, The patient faces the wall, resting her elbows against it. *E* and *F*, The pelvis is tilted forward until the symphysis touches the wall. The heels remain on the floor, and the knees are kept straight.

it done. She had four hypnotic treatments, which were followed by a painless period. Several additional treatments before the succeeding period gave complete relief from the dysmenorrhea for the year that the patient was observed. The number of treatments required in other cases varied from one to twelve. The striking results obtained in this series certainly warrant further trial of this method of treatment in cases that do not respond to the usual therapy. For a discussion of the hypnoanalytical method of therapy, the reader is referred to an article by Kroger.

Alice Clow was one of the first to emphasize what could be accomplished by mental and physical hygiene. She was able to reduce the incidence of dysmenorrhea 70 per cent in the girls' school in England where she made her study. She prepared them mentally by explaining the physiology of menstruation, emphasizing that it was a normal process and was not necessarily accompanied by pain or disability. The use of the terms ''unwell,'' ''the curse,'' and others were discouraged because of their unsound implications. Warm showers or sitz baths and moderate exercise were advised and laxatives given as needed. Special exercises such as the knee chest, bending, twisting, rowing, swaying, and others were recommended.

On the basis of the work of Ayer and Ussher, Billig emphasized the role of fascia contraction in dysmenorrhea and suggested stretching exercises to correct this condition. Exercises were used by Haman in the treatment of 129 females between the ages of 15 and 37 years, all having severe dysmenorrhea requiring bed rest at the period time. The exercises are very simple to perform, they take less than five minutes a day, require a minimum of space, may be done at home, and need be carried out usually for only two or three months before improvement results. Fig. 973 illustrates these exercises.

Each position is assumed three times, and all are repeated three times a day. If, at the end of two or three months, sufficient relief is obtained, the exercises are discontinued for one or two months. Some patients have no recurrence of pain at catamenia; in others, where relapse occurs, the exercises are performed once daily for one week before the period is due, as a prophylactic measure. The patients in this series were followed for 2 to 20 cycles after they started doing the exercises, the average being 6.5 cycles.

There was at least some degree of relief in 85 per cent of all patients treated. If we consider only those suffering from the primary form of dysmenorrhea, the percentage of relief was 89.3 per cent.

Dietary elements which have been shown to help are vitamins and calcium and caloric regulation to increase or decrease weight.

During the course of treatment of menorrhagia with vitamin K by Gubner and Ungerleider, the finding of relief from dysmenorrhea was not anticipated, but in the series of 43 patients relief of dysmenorrhea was noted in approximately two-thirds of the cases treated. Since it is believed that the immediate cause of cramps accompanying menstruation is the presence of a foreign body in the uterine cavity, a clot in this instance, which has the effect of stimulating the uterus to contract, the establishment of a normal flow may explain the relief from pain in these cases. Vitamin B has been shown to be necessary for the proper destruction of estrogen by the liver. Boynton and Hartley obtained complete relief of symptoms in 67 per cent of their

dysmenorrheic women at the University of Minnesota by the use of calcium gluconate and viosterol. Calcium gluconate 60 grains daily for two weeks before the period gave relief.

The importance of general nutrition for proper endocrine functioning has been clearly shown experimentally and clinically. The thin, studious, sedentary girl and the overweight girl are both prone to suffer with dysmenorrhea. A reducing or building-up diet should be given as indicated.

The **myogenic factors** responsible for dysmenorrhea have been discussed under Etiology, and various antispasmodic and relaxing drugs have been used. Bickers obtained the typical type of tetanic contraction in 13 of the 15 dysmenorrhea cases studied. Tetany was never seen in the nonpainful menstrual contractions. After testing the action of many drugs and hormones on uterine contractions, he found that only morphine and Pavatrine (a nonnarcotic synthetic spasmolytic) were able to abolish the uterine spasm. He employed this drug clinically and found it effective in 67 per cent of his dysmenorrhea cases, when given orally. One tablet is given to determine the tolerance of the patient, and thereafter one to two tablets three to four times a day as needed. It is best to start administration three to five days preceding menstruation.

Another nontoxic spasmolytic agent, Depropanex, was used by Grossman in a group of twenty-five patients. The dose varied from 1.5 to 4 c.c. given intramuscularly. Relief usually occurred within fifteen minutes. Complete relief was obtained in his group of private cases in 79 per cent and partial relief in 17 per cent.

The **neurogenic factors** causing dysmenorrhea have been investigated by Kieffer et al. He found that stimulation of the internal os caused uterine contraction, cervical spasm and pain, and he feels that the spasmodic pain experienced in cases of dysmenorrhea may be due to an abnormal state of the cervical ganglia. This theory has received support from the practical work of Blos and also of Kennedy. The former cured 90 per cent of his dysmenorrheic patients by injecting the cervical ganglia with 70 per cent alcohol. Birnberg demonstrated a positive prolan response after gradual cervical dilatation in 23 of 30 women within thirty hours, and felt that the pituitary was stimulated through the sympathetic nerve pathway. Bertrand et al. demonstrated changes in the electroencephalogram in 11 of 13 women after cervical dilatation, curettage, or swabbing of the uterine cavity. Certain drugs are used for their effect on the nerves. Hundley, using benzedrine sulfate, reported complete relief in 61 per cent of 186 attacks, using one or two 10 mg. doses. Atropine, Syntropan, Trasentine, Edrisal, have all been used with encouraging results. Ainlay obtained good results using a capsule containing aspirin 5 grains, Phenacetin 3 grains, and Propadrine hydrochloride ¾ grain.

Priscoline, a powerful sympathetic vasodilator, was used by Greenblatt et al. to counteract the muscular ischemia with fair results, but the side effects complicated its use. Bickers used pitressin tannate in oil intramuscularly to desensitize the patient to pitressin and render the vascular bed of the myometrium unresponsive to the patient's own posterior lobe hormone stimulation. In intractable cases of dysmenorrhea of any type where all conservative

measures have failed, relief can usually be obtained by resection of the presacral nerve as recommended by Cotte, Leriche, Wetherell, Behney, and others.

Endocrine Therapies.—Before discussing the hormones specifically concerned with pelvic physiology it would be well to mention two of the general metabolic hormones which have been found to relieve dysmenorrhea. These are thyroid and insulin.

Most of the thyroid cases with associated dysmenorrhea have a lowered metabolism and, by administration of thyroid alone, the pain frequently disappears. On the other hand, cases of interstitial thyrotoxicosis with an associated dysmenorrhea are occasionally cured when the thyrotoxicosis is treated and the overactive thyroid function corrected. Iodides and bromides are the drugs used.

It has long been known that there is a high incidence of dysmenorrhea among undernourished individuals. Quite by accident, Altschul, while using insulin to treat a group of undernourished patients, found that the pain in dysmenorrheic patients was relieved. He then gave it to a series of *normally nourished* dysmenorrheic women and found that 10 of the 12 women treated were relieved. Tedstrom and Wilson obtained relief of dysmenorrhea patients by high carbohydrate feeding and concluded that the relief was due to the stimulating effect of the carbohydrate therapy on the pancreas, causing it to secrete extra insulin. Schrick obtained equally excellent results using 5 units of insulin before lunch daily starting three to five days before the onset of the period and continuing through the period.

In regard to specific hormones, as previously mentioned, treatments using the ovarian, testicular hormones and the chorionic gonadotrophins are based on confusing and, in some cases, diametrically opposed etiologic bases; hence, I shall merely discuss therapy from an empiric standpoint.

ESTROGENIC THERAPY.—The hormone therapy which seems to be the most logical and to give the most consistent results is the one suggested by Sturgis and Albright. Based on the knowledge that primary dysmenorrhea rarely occurs in patients having anovulatory cycles, these workers were able to prevent ovulation and relieve the pain in 25 cases of severe, disabling dysmenorrhea by giving 10,000 I.U. of estradiol every day for six days, giving the first dose before the sixth day of the cycle. Since their early report, many others confirming these results have appeared. Sturgis and Meigs were able to prevent periods for as long as three months by giving estradiol dipropionate 10 mg. on the sixth day and repeating it at ten-day intervals. Randall and Odell used 1 mg. of diethylstilbestrol daily for twenty days starting on the second day of the cycle. Haus et al. got their best results by using a total of 60 mg. diethylstilbestrol or 75 mg. Premarin. Schuck, in a study of 790 cases of dysmenorrhea among students at New York University, obtained relief in 60 per cent of 300 cases of primary dysmenorrhea using Estinyl 0.05 mg. daily for 10 or 12 days, starting on the first day of the cycle. They state: "No other medication had a comparable effectiveness."

Dignam, Wortham, and Hamblen found that the effect of estrogens in suppressing ovulation in any case was unpredictable, yet all patients receiving a daily dose of 3.75 mg. Premarin from the fifth to the twenty-fourth day were relieved of pain. Doses of Premarin 0.625 mg. for the same period pre-

vented ovulation only half of the time. This indicates that the estrogen may exert a beneficial effect on the uterine muscle, especially when the uterus is hypoplastic. Results with estrogen are not permanent, hence treatment must be repeated each month.

PROGESTERONE THERAPY.—In view of our present knowledge of the effects of the various hormones on uterine muscle and the fact that prevention of ovulation and corpus luteum formation relieves dysmenorrhea in close to 100 per cent of the cases, it seems strange that some reports claim good results with an occasional case relieved for months. The dosage schedule is 1 to 5 mg. of progesterone intramuscularly, daily or every other day for a week preceding the period. Lackner et al. obtained their best results in women with large uteri. If the sublingual preparation is used, 10 to 20 mg. are given daily for a week before the period.

ANDROGEN THERAPY.—When the androgens were first introduced, numerous articles appeared on its use in dysmenorrhea, but in recent years most men have discontinued using it for this condition, both because of its undesirable side effects and because estrogen therapy is better and less expensive. The dose suggested for androgen therapy is 10 mg. of sublingual methyl testosterone daily for ten days preceding the period.

SECONDARY DYSMENORRHEA

The **pelvic lesions** most frequently causing dysmenorrhea are endometriosis and adenomyosis, ovarian cysts, pelvic inflammatory disease, and occasionally uterine displacements.

With endometriosis, the ectopic bits of endometrial tissue menstruate with each period, forming hematomas filled with the typical chocolate-colored material. Since there is no avenue of escape for the menstrual discharge, these isolated glands become markedly distended with each period and the distention causes pain. The pain in this condition usually is most marked just before and during the period.

Payne in a series of 307 cases of endometriosis found that he was able to determine the onset of the pain in relation to the period in 92 patients. He found that 93 per cent had the pain before or during the period. The pain is described as ''boring or grinding'' in character. In adenomyosis of the uterine wall the pain is usually most severe in the latter part of the period and for a day or so after the period.

In an attempt to determine the importance of the uterine position as a cause of dysmenorrhea Bell and Parsons made a study of the women students at the University of Michigan.

Of the 840 women students 12 per cent complained of severe dysmenorrhea. Of the 12 per cent the uterus was retrodisplaced in 43 per cent, it was acutely anteflexed in 9 per cent, while in the remaining 48 per cent the uterus was in normal position. Twelve of the dysmenorrheic women required opiates for relief at the menstrual time, and, in these the uterus was retroflexed in seven, acutely anteflexed in one, and in normal position in the remaining four.

A trial of pessary treatment is helpful in determining whether in a given case the retrodisplacement is the factor causing the pain. If a pessary cannot be fitted, the knee-chest posture will relieve some cases.

Ovarian dysmenorrhea, according to Browne, is a definite clinical entity which can be differentiated from uterine dysmenorrhea by passing a sterile sound into the uterine cavity and noting the type of pain resulting. With the uterine type, the pain is referred to the suprapubic area or lower abdomen, while with the ovarian type the passage of the sound is almost painless. Browne found that sclerocystic changes of the ovary were constant in severe ovarian dysmenorrhea.

Extrapelvic lesions in which dysmenorrhea is occasionally a symptom are ureteral strictures and a chronic appendiceal irritation in a low-seated appendix. Hunner of Baltimore was the first to call our attention to ureteral strictures as a frequently overlooked cause of dysmenorrhea,

In 1939 Sears reported 14 cases in which dilatation of the ureteral stricture cured the dysmenorrhea. Most of these patients had had operations either for chronic appendicitis or salpingitis.

In cases in which severe nausea and vomiting are associated with the dysmenorrhea, a low-seated appendix which hangs down in the pelvis should be ruled out. We recall two such cases in particular in which simple removal of the appendix gave the patients complete relief. In one of these the appendix was so firmly attached to the ovary that a small wedge of ovarian tissue had to be taken in order to remove the appendix. Previous dilatation had not helped in this case.

Mechanical obstruction, because of a pin-point opening, stricture, tight internal os, acute anteflexion, polyp or fibroid, is the cause of pain in some cases. The exact mechanism of the relief secured by dilatation is not known but two theories are advanced:

a. Relief of tension in the uterine cavity. It seems reasonable to assume that the increased tension from stenosis would tend to make the uterine contractions painful, as it does in the intestine and other hollow organs.

b. By the mechanical dilatation stimulating ovulation, as does an electric current in the canal. This seems opposed to the general assumption that non-ovulatory menstruation is painless.

The diagnosis of the obstructive factor in the complex symptomatology is made from the abrupt onset of severe cramping pains just preceding the flow and their relief when the flow is well established, along with the usually associated small cervix and small cervical opening.

The technique of office dilatation consists in gently introducing graduated dilators past the internal os under antiseptic precautions, starting with a small size and advancing to the largest that can be easily introduced. It is well to leave the last one in the dilated cervix for several minutes. In married women, the dilatation is carried out in the preovulatory interval. E. L. Stone, in reviewing the various treatments for primary dysmenorrhea, concluded that his best results were obtained by dilatation.

If a patient obtains temporary relief by office dilatation, then it is probable that a more lasting result will be secured by thorough dilatation under anesthesia followed by the insertion of a hard rubber stem (Fig. 974) or the soft thick-walled rubber-tube stem (Fig. 975).

RUBBER-TUBING STEMS.—In an endeavor to maintain the secured dilatation practically to the full extent for the first week or two, we employ thick-walled rubber tubing which fits the secured dilatation, instead of the regular hard rubber stem. Three sizes of pure gum

rubber tubing are on hand for this purpose, the largest being ½ inch in diameter (outside measurement), about ⅛ inch wall thickness and 3/16 inch hole, and the other two 7/16 inch and ¾ inch outside measurement, respectively. Pieces 1½ inches long are cut, and one end is rounded to facilitate introduction. These are sterilized and kept ready for use in cases of dilatation for obstructive symptoms (Fig. 975, *A*).

This rubber tubing with thick walls as specified has the advantages that (a) it is stiff enough to maintain practically the full dilatation secured, (b) the central opening allows escape of fluid and prevents back pressure during uterine contraction, which is a necessary
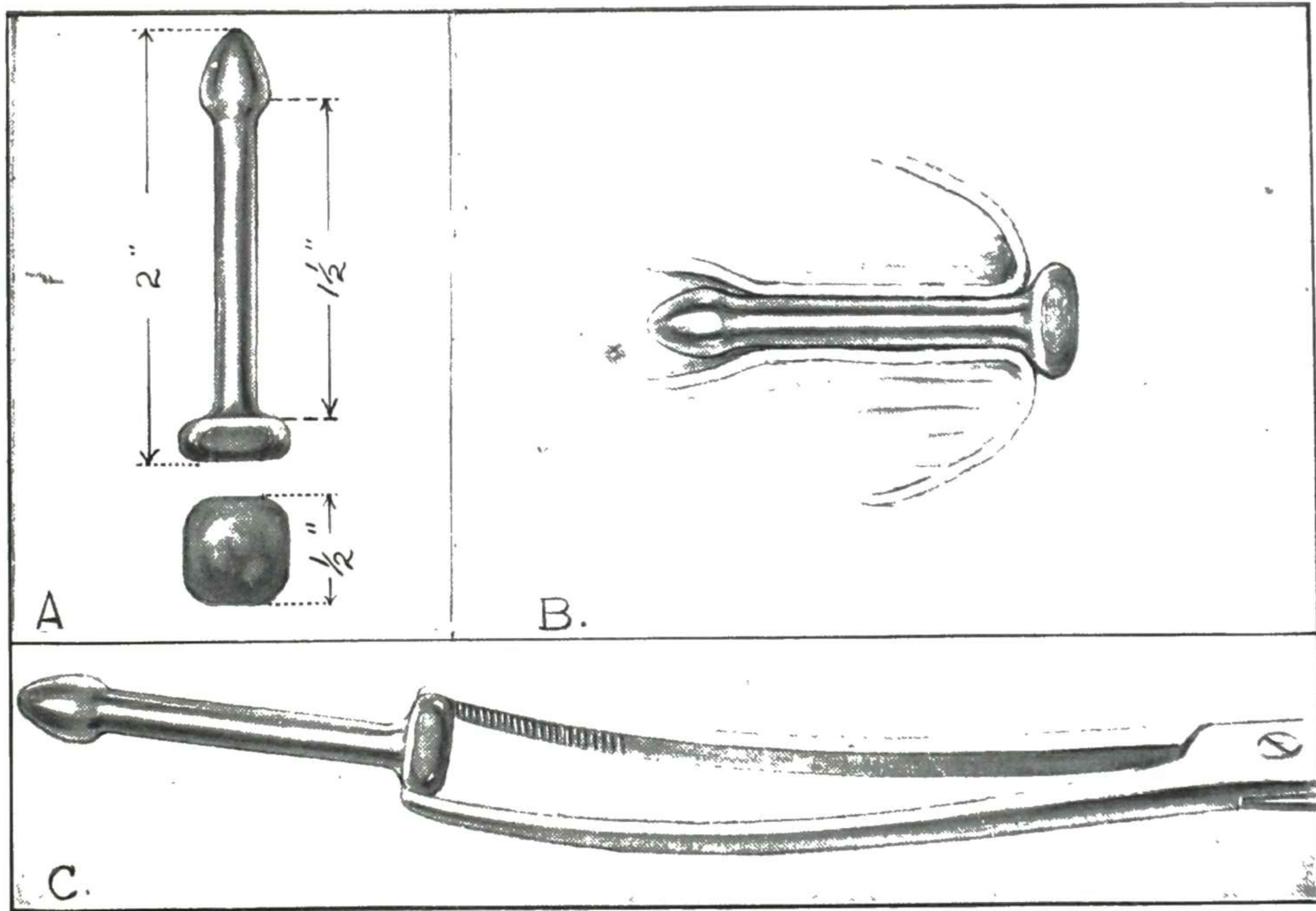

Fig. 974.—Improved stem of hard rubber, for use in the cervix to maintain a good-sized canal after dilatation for stenosis. *A*, Dimensions of stem. *B*, Stem in place in dilated cervical canal. *C*, Showing the use of the flattened areas on the base, by which the stem may be grasped with a forceps for introduction or for removal.
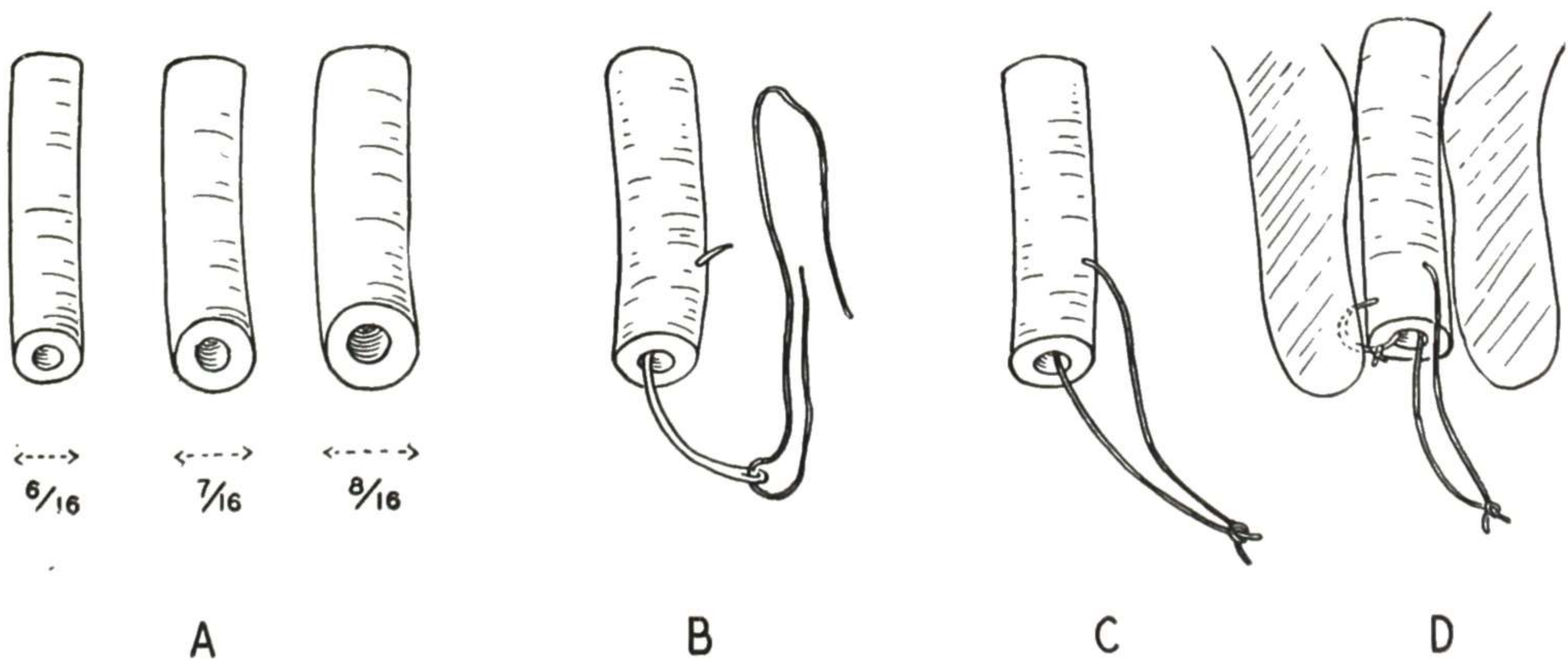

Fig. 975.—Rubber-tubing stems. A piece of thick-walled rubber tubing is used, instead of the usual hard-rubber stem, to maintain better widening of the internal os after dilatation for the obstructive factor in dysmenorrhea. *A*, Three sizes of rubber-tubing stems. They are 1½ inches long, with one end rounded to aid introduction. They are cut from three sizes of rubber tubing, the wall of each being about ⅛ inch thick and the width (outside measurement) being ⅜ inch, 7/16 inch, and ½ inch, respectively. The size is selected to fit the dilatation secured, so as to maintain that dilatation to the full extent as far as practicable. When in place, the upper end of the stem should be well up past the internal os, and the lower end should be slightly *inside* the cervix, so as to avoid irritation of the vaginal wall.

provision when trying to maintain such wide dilatation, (c) the size may be selected to fit the extent of dilatation secured, and (d) rubber tubing is always at hand, as it may be easily secured in required sizes at small expense.

After securing the full dilatation which is safe in that case, the size of rubber-tubing stem is selected to fit that dilatation. To facilitate removal it is well to pass a piece of strong braided silk through the wall of the tube well up from the end. A large Mayo needle threaded with the silk is passed inside the tube (Fig. 975, B) and out through the wall. The two ends are then tied together to form a strong loop, as in Fig. 975, C, which may be grasped for removing the tube. The tube is then dipped in A-G solution (I per cent solution
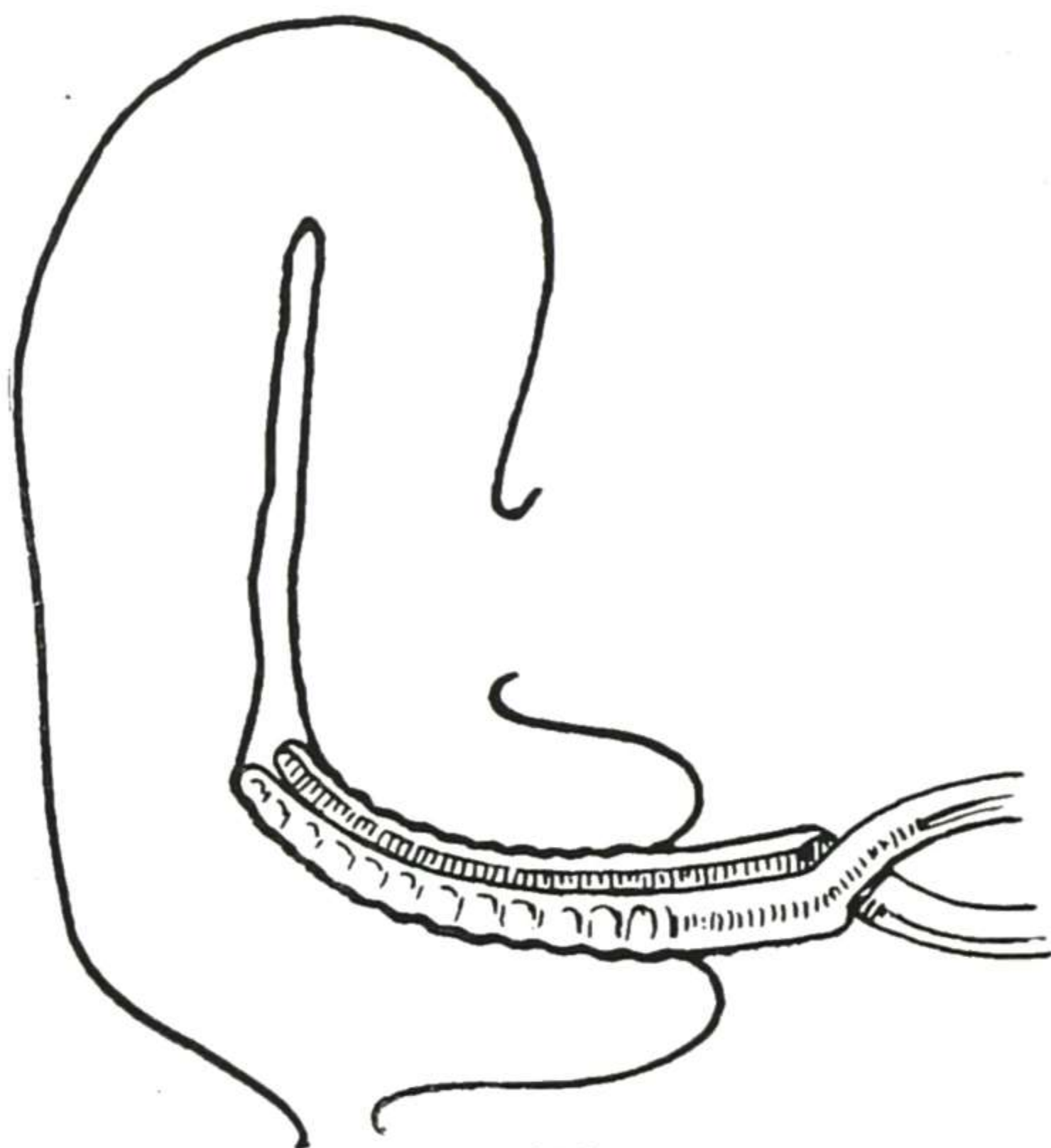

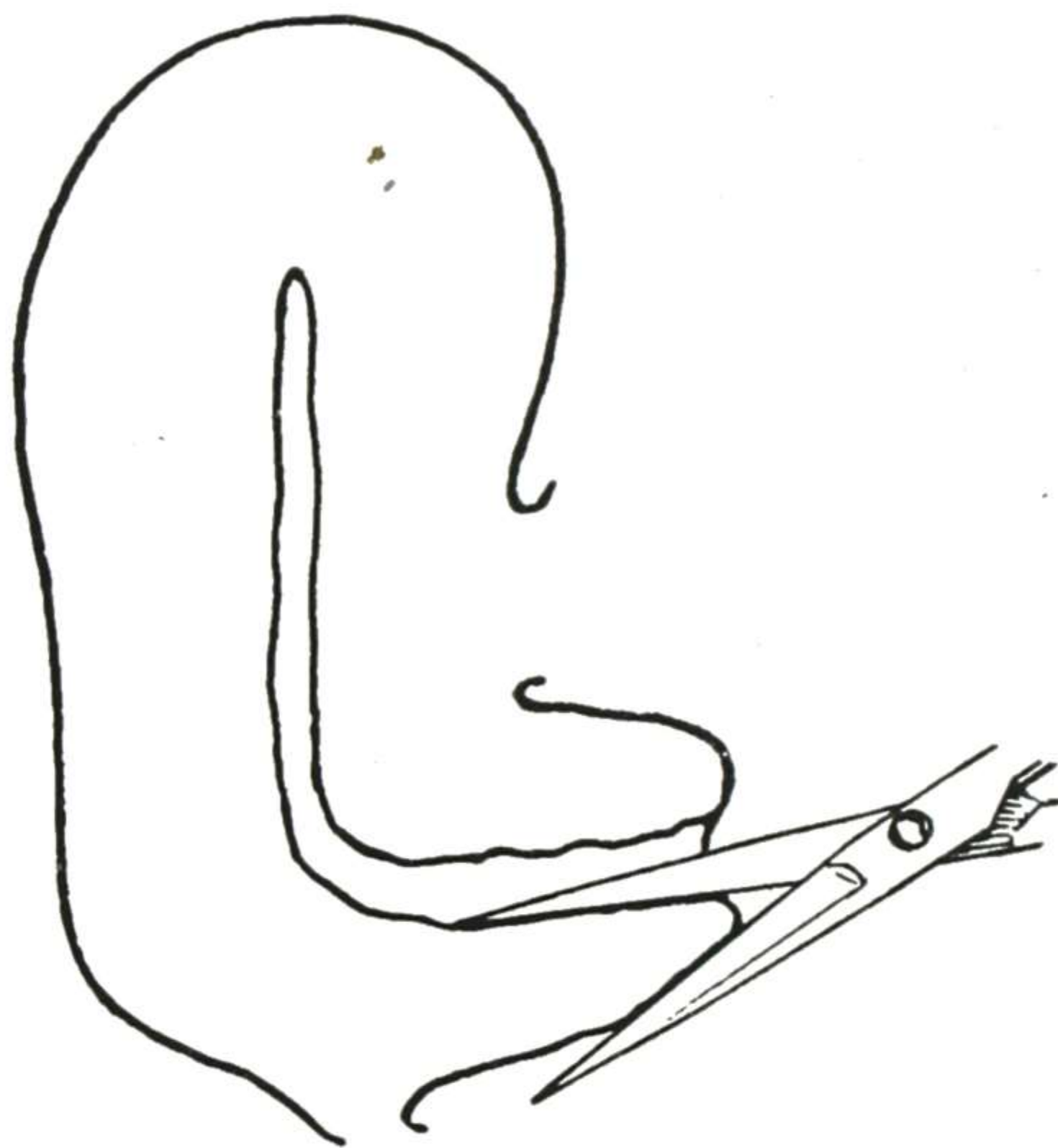Fig. 976.   Fig. 977.

Fig. 976.—Dilating the cervix, which is the first step in the operation of posterior division of the cervix.

Fig. 977.—The scissors in place for division of the posterior wall of the cervix. A strong pair of sharp scissors is most convenient for this division, though a knife may be used if preferred. The higher division is preferably made with a knife, as shown in the next illustration.

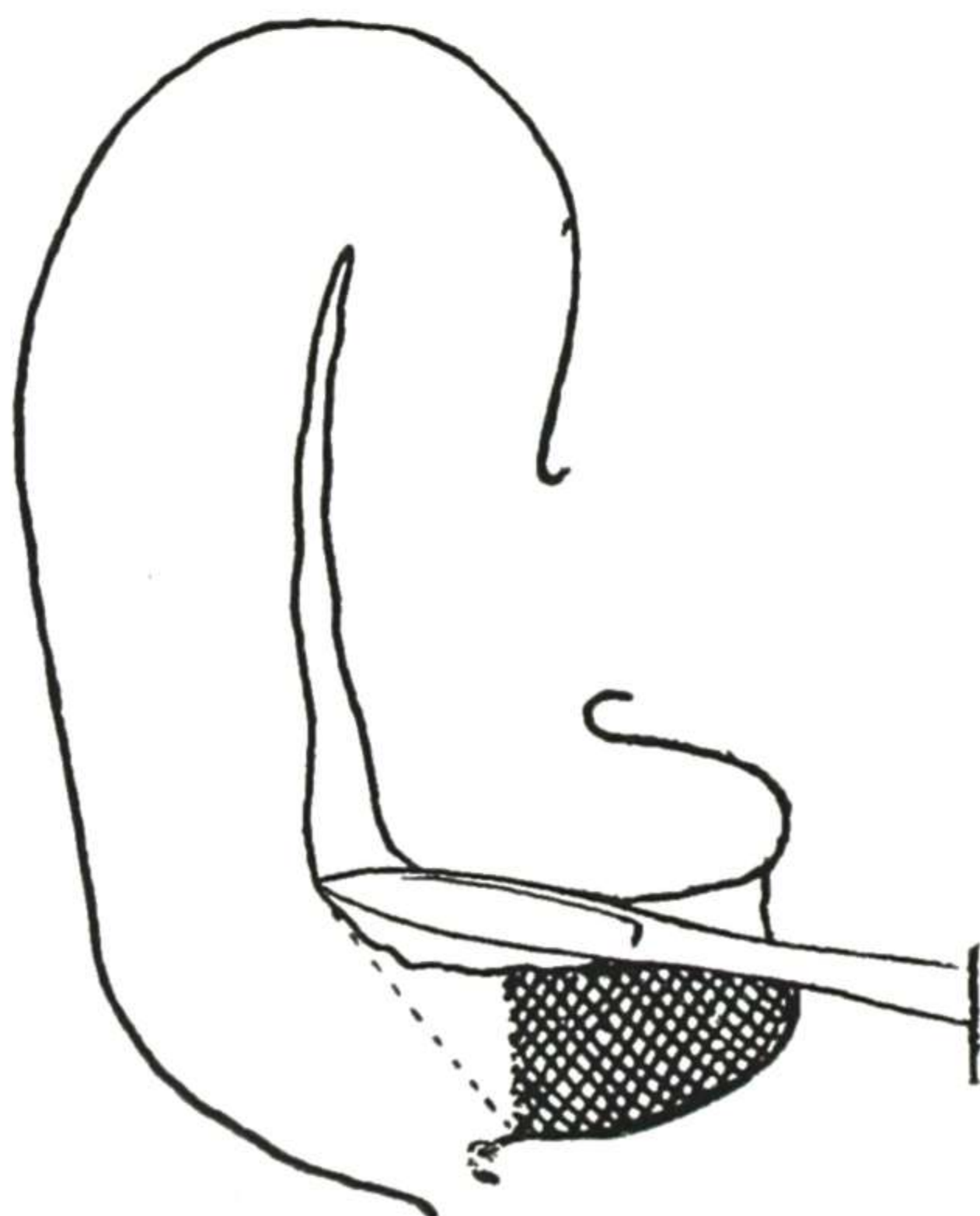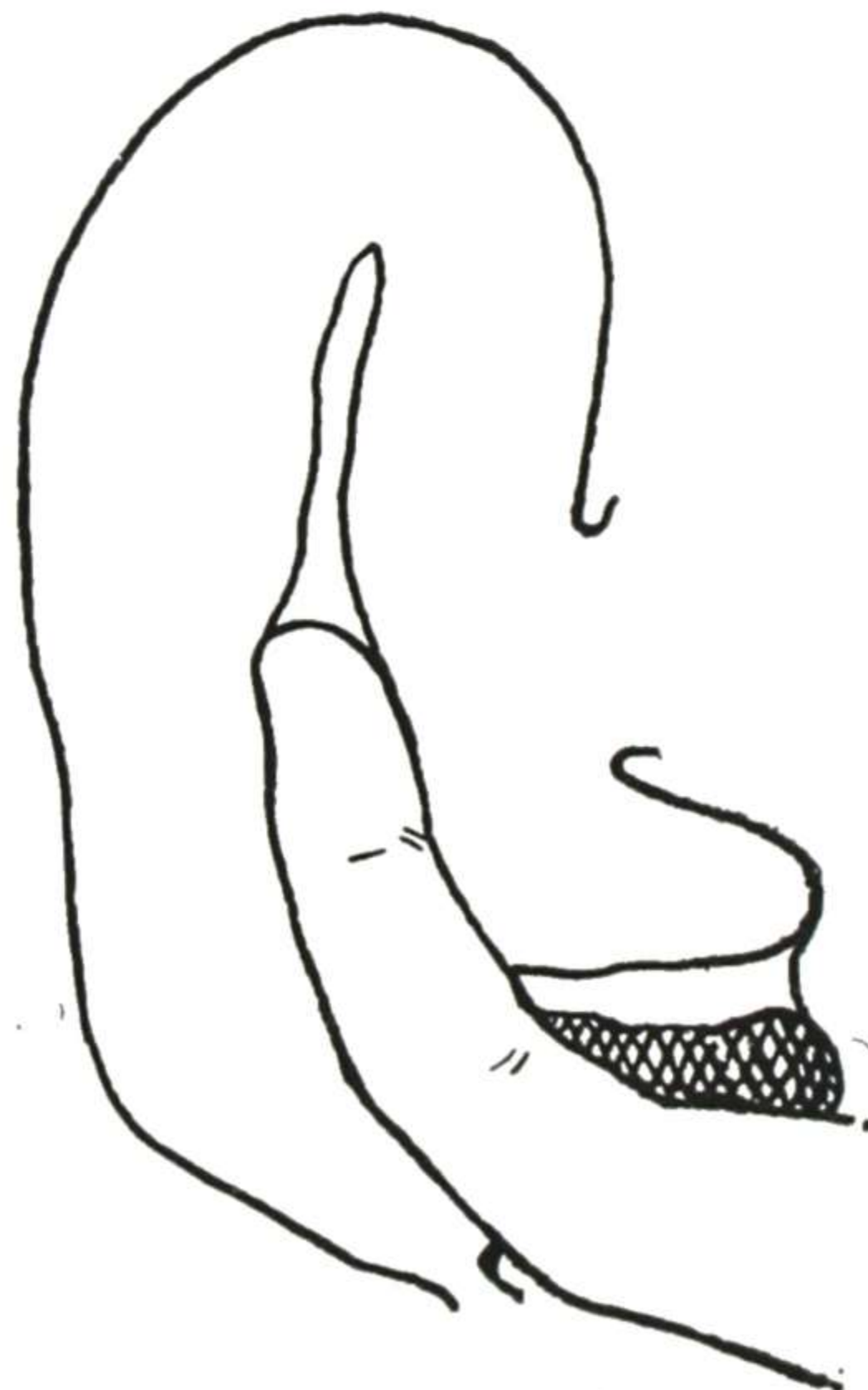Fig. 978.   Fig. 979.

Fig. 978.—Completing the division of the posterior wall up past the internal os. The dotted line indicates the limit of the necessary division. This division of tissue by the knife is made a little at a time under the guidance of the finger.

Fig. 979.—The necessary division of tissue completed, permitting the finger to be passed up through the internal os.

of neutral acriflavine in glycerin) for lubricating and antiseptic effect. After introduction well past the internal os, the tube is fastened in place by a suture through it and including the cervical wall (Fig. 975, *D*). The large soft rubber stem should be left in place for a week. In a severe case, it is well to leave the stem in place in the uterus until after the next menstruation, if the patient can be kept under observation so that the stem may be removed should any symptoms of irritation develop.

Thorough dilatation and curettage and the stem give marked relief in most cases. They should be followed, of course, by treatment to overcome the other features in the case, namely, the endocrine disorder and the hypersensitive and hypercontractile uterine muscle. The duration of satisfactory widening of the canal is variable, usually continuing at least several months and sometimes several years or indefinitely. Though there is a tendency to return gradually toward the former condition, the narrowing of the canal seldom becomes as troublesome as before the dilatation.
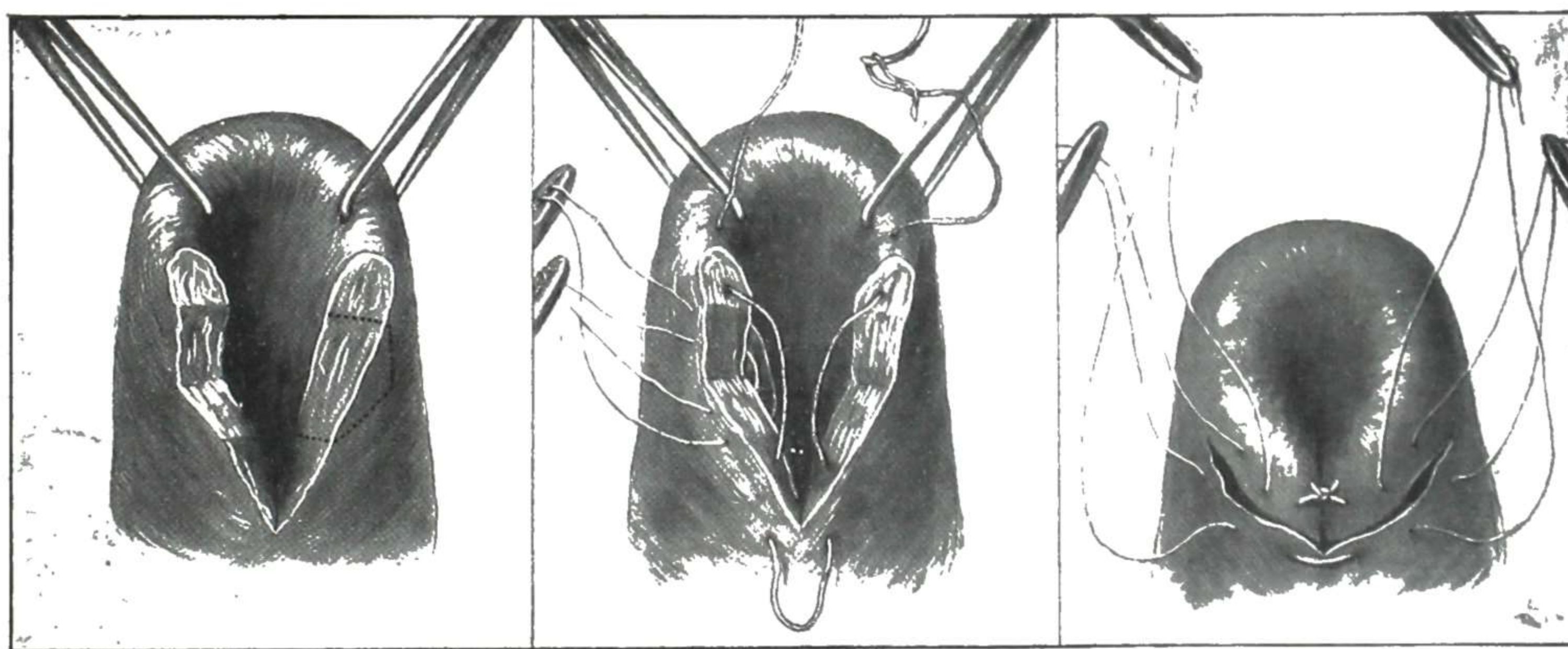

Fig. 980.   Fig. 981.   Fig. 982.

Fig. 980.—The posterior wall of the cervix divided. The wedge of tissue has been removed from one lip and the wedge to be removed from the other lip is shown in dotted outline.

Fig. 981.—The sutures for closing the wound. The central approximation suture is in place and also the lateral hemostatic sutures on one side.

Fig. 982.—The central approximation suture tied, bringing tissue into the angle of the incision to keep the internal os open.

In the exceptional cases in which the obstructive feature again becomes severe, relief from obstruction may be given by a special plastic operation on the cervix. This consists of splitting the cervix posteriorly and then sewing it in such a way as to maintain widening of the canal at the internal os. This operation, devised many years ago by Dudley, has proved effective in most of these exceptionally troublesome cases. The operation, however, must be carried out accurately, keeping in mind that the essential point is permanent enlargement of the internal os. The technical details of the operation are shown in Figs. 976 to 982. The steps of the operation are as follows:

a. The cervix is dilated thoroughly and the uterus curetted in the usual way.

b. The posterior lip of cervix is then split longitudinally up to the vaginal vault, the incision being carefully continued internally up to and past the internal os. The constricting ring about the internal os should be divided sufficiently to admit a finger readily. Care is necessary to avoid cutting too deeply into the uterine wall at this point, for, if the wall is cut through and the peritoneal cavity opened, there is danger of peritonitis. Ordinarily, there is no necessity for opening the peritoneal cavity. In some cases, however, the posterior peritoneal pouch comes very low or the internal os is situated unusually high. In either case, it may be advisable deliberately to open the peritoneal cul-de-sac in order to complete the operation properly. The division of the intravaginal portion of the cervix may be most conveniently made with long scissors (Fig. 977). The careful division of the ring about the internal os is made with a bistoury under the guidance of the finger (Figs. 978 and 979).

c. A wedge of tissue is then cut out of each lip, as indicated by the dotted lines in Fig. 980, so that each of the two cut edges will fold well on itself when the principal suture is tied.

In recent years it has been shown that many of the allergic reactions are produced by histamine, and many workers have obtained relief of symptoms by antihistamine drugs. Muether et al. have reported relief of a large majority of cases of dysmenorrhea by using histaminase, a physiologic antagonist of histamine, and McElin and Horton obtained relief in 50 per cent of their cases by using Benadryl. In the cases where allergy seems to be a factor, one of the various antihistamines should be tried.

PREMENSTRUAL TENSION

Much has recently been written about premenstrual tension. About one-half of all women experience a group of symptoms designated as molimina, which include increased nervousness or irritability, fullness of the breasts, and slight bloating of the abdomen, with some slight pain. In most women these symptoms are very mild and are considered a normal part of menstruation; however, in a large number of women these and other symptoms are of a severity that results in marked disability. This exaggerated type of menstrual response has been designated as premenstrual tension, and the symptoms begin ten to fourteen days prior to the period, reach their peak shortly before the period, and disappear rapidly with the onset of the period. The symptoms included under this term include headache, emotional disturbances with irritability and depression, fullness or pain in the breasts, abdominal bloating sometimes accompanied by pain, and nausea or vomiting, and sometimes edema of the extremities. In some cases there is an increased sex desire; Thorn et al. noted an increased thirst; Morton found that a hypoglycemia was frequently present and the patients had a craving for sweets, and some complained of trembling of the hands which they usually called the "shakes." In emotionally unstable women, the mental confusion may simulate any of the functional nervous disorders.

The underlying cause of these symptoms is an abnormal water metabolism with retention of the sodium ion. Various etiologic factors causing this water retention and edema have been proposed. Greenhill and Freed felt that with the increase of sex steroids in the blood prior to the onset of the menses there was an accompanying retention of the sodium ion, resulting in edema in the tissues of the body. The mental symptoms were due to a mild edema of the brain, the bloating, nausea, and vomiting to an edema of the intestinal wall, and so on. Bickers, in a careful study of 22 such patients, found an average gain in weight of 6.8 pounds in the premenstrual period, whereas in normal patients the gain was less than 2.5 pounds, and the water loss during the first twenty-four hours of menstruation was almost three times that of the normal patients. An excess of estrogen or a deficiency of progesterone in the blood or a disturbed estrogen-androgen balance have all been suggested. The Biskinds postulated a vitamin B deficiency, while Argonz and Abinzano recommended high vitamin A therapy, using 200,000 I.U. daily during the second half of the cycle. The role of edema has been reviewed by Taylor, and also by Miller, and there can be no doubt of its importance in interpreting many of our hitherto obscure syndromes.

The psychosomatic element in this as well as in many other gynecologic conditions is extremely important, and for an excellent article on the use of hypnotherapy in these conditions the reader is referred to one by Kroger.

Treatment of the premenstrual syndrome in most cases gives striking relief; it consists of a salt-free diet for two weeks before the menses, with ammonium chloride 7½ to 15 grains three times a day during this period. If the patient cannot tolerate the ammonium chloride, Bickers recommends pyrilamine 8-bromotheophyllinate (Bromth) 50 mg. three times a day for ten days before the onset of menstruation. Various resins have been tried, but, because of the care necessary to prevent a disturbance in the potassium ion metabolism and the expense, these are not as desirable as those mentioned above. Morton, in addition to the above, gives a high-protein, high-carbohydrate diet with frequent feedings to control hypoglycemia; and, to correct what he feels is an estrogen-progesterone imbalance, he advises 500 to 1,000 units of chorionic gonadotrophin twice a week for the two weeks prior to the period to increase the secretion of progesterone.

MENSTRUAL HEADACHE

In a patient inclined to headache, the menstrual period is the favorite time for the most troublesome manifestation, as it is for many other disturbances of the nervous system. There is not space for a general differentiation of the various types of headache which may occur at the menstrual time. The disturbed water balance has been mentioned, and it is advisable to call attention to another troublesome type, which has recently been elucidated with considerable relief to the patients so afflicted. This type is characterized by exostoses on the inner table of the skull in the frontal region (Fig. 242) with resulting pressure on the "silent area" of the brain.

This condition is of interest to gynecologists in that it is the cause of one of the severe types of menstrual headache (often with visual disturbances) and not infrequently there are other menstrual disturbances, such as excessive flow or amenorrhea. Another point of interest is that the pelvic and other symptoms closely resemble those ordinarily associated with certain cases of pituitary dysfunction, and this diagnosis is very likely to be made and the exostosis overlooked.

The details of this condition were worked out by Dr. Sherwood Moore, professor of Radiology, Washington University School of Medicine. He investigated very extensively these inner-table exostoses, the resulting clinical symptoms, and associated bodily changes, and has called attention to their importance in an article (see references).

The symptoms listed by Moore as characteristic of this condition are: (1) Headaches, often disabling. Cranial tenderness with sometimes a feeling of pressure. (2) The obesity may be extreme and is of the rhizomelic type. (3) Visual disturbances of various types. (4) Easy fatigue and muscular weakness. (5) The breasts are usually larger and more pendulous than they are in women who do not have hyperostosis of the skull. (6) Hair growth on the chin is common. (7) Mental dullness, dizziness, depression, and poor memory. (8) Epileptiform-like seizures. (9) Cranial nerve disturbances. (10) Regional sensory and motor disturbances, tingling, numbness, transitory hemiplegias and hemiparesis.

One of the clinical features of diagnostic importance is the fat distribution just to the middle of the upper arm and to the middle of the thigh. This is shown in Fig. 242, which is a photographic study from Dr. Moore's collection. The sella turcica was normal.

We have had several patients with this disorder. Dr. Carr, of the Department of Neurology, obtained complete recession of troublesome symptoms in some of them on a diet high in gelatin.

INTERMENSTRUAL PAIN AND SPOTTING

The interesting subject of pain occurred at a certain time every month in the intermenstrual period has received considerable attention from investigators, and the conclusion has been reached that it is not an indication of any particular lesion.

Malcolm Storer, who reported 20 cases of his own and 25 additional cases collected from literature, found that in 10 of the cases there was a marked increase in the leukorrhea at that time, indicating congestion of the uterus. There may be a slight bloody flow at this time. In the 45 cases reported by Storer the pain appeared with regularity in all cases, practically every month unless pregnancy was present. In 22 cases it appeared always at the same time (in most cases about two weeks) after the beginning of the last menstrual flow. In 13 cases there was a variation of two days, in 4 cases there was a variation of four days, and in 2 cases of irregular menstruation it would appear on a certain day before the menstruation. In 37 out of 41 cases the pain appeared from twelve to sixteen days after the beginning of the last menstruation and in 20 of them it began exactly on the fourteenth day. In 2 cases it came from the seventh to the tenth days, in 1 case on the seventeenth day, and in 2 cases on the eighteenth day. Observations like these well support the view now generally held that this periodically returning pain, often alternating in the right and left sides from month to month, is actually caused by the enlarged graafian follicle at the time of ovulation. It seems plausible that under certain conditions this process might be associated with pain.

Wharton and Henriksen in a study of 61 cases, thirty of which were subjected to laparotomy, found no consistent factor causing the pain. In nine patients there was some free blood in the pelvis. Where the condition was severe enough to warrant it, they found that the only uniform method of relieving the pain was removal of one or both ovaries. They point out that pain with ovulation frequently led to a mistake in diagnosis, with unnecessary operations, especially when confused with the symptoms of acute appendicitis. McLaughlin in a later study of 57 cases confirmed these findings.

This pain in the mid-interval ("Mittelschmerz"), often accompanied with a slight show of blood ("spotting"), is probably more common than we realize, for Papanicolaou found microscopic blood in about 25 per cent of women examined at the ovulation time. This, as well as the pain, is probably due to the temporary drop in estrin and inadequate progesterone secretion to prevent a little blood loss. As the progesterone and estrone levels increase with the maturing corpus luteum, the bleeding and pain stop. This would indicate the administration of progesterone and estrone as the painful time approaches. Pelvic heat is a helpful adjunct to any other treatment during the pain.

Radiation has been used successfully, both x-ray and radium. In persistent cases Keene used 100 to 200 mg. hr. of radium, and in so doing he obtained the double benefit of dilatation and mild radiation effect on the ovaries.

MENSTRUAL PRURITUS

Menstrual itching and irritation about the vulvar and anal areas may be due (1) to congestive aggravation of some continuing skin lesion such as

acne or eczema, (2) to herpes or fungus infection appearing at that time, (3) to allergic reaction to pad material or powder or soap or other article used locally, (4) to local reaction to special medicine or food, or (5) to allergic reaction of the patient to her own menstrual blood. (6) In addition, Kroger points out that it is a well-established fact that genital tensions frequently find their motor outlet by way of pruritus vulvae. Masturbation in sexually frustrated individuals is common, and, in those who do not masturbate, the dammed up genital excitement may result in pruritus. Treatment consists in sublimating the sex drive in work, sports, and other interests, and, in some cases, in psychotherapy. Long engagements should be avoided.

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Chapter 14
STERILITY AND SEXUAL DISTURBANCES

The disturbances belonging in this chapter will be taken up in the following order:

> Sterility.
> Contraception.
> Sterilization.
> Dyspareunia.
> Sexual Frigidity.
> Sexual Hyperesthesia.

STERILITY

The problem of sterility has become one of increasing importance in gynecology. The estimates by different authorities of involuntary sterile marriages vary from one in ten to one in six. The need for detailed study of the various aspects of the problem by men in many related fields who were especially interested in barren couples led to the formation in 1944 of the American Society for the Study of Sterility. A small booklet prepared by their Research Correlating Committee, *Evaluation of the Barren Marriage*, enumerates the minimal procedures required and may be obtained from this organization for a nominal sum.

In recent years the heretofore underestimated male responsibility has been emphasized. This percentage ranges from 30 per cent in some series to 48 per cent in others. Only a small number of cases show a single lesion which can be held entirely responsible for the sterility. Usually there is a combination of lesions in the wife or husband or both, any one of which would probably not render the couple sterile; but their combined influence is enough to bring about that result.

It is usually the wife who seeks consultation on this problem because for some reason the couple assume that inability to conceive must be due to some feminine inadequacy. The physician on the first visit should explain with an understanding and sympathetic interest the various factors involved and should give the patient some estimate of the number of visits and tests needed and an approximate estimate of the expense so that the couple will not become discouraged after several visits. A conference should be arranged at which the problem can be discussed with both husband and wife so that they can both be aware of the need for a combined investigation. This will frequently

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