

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

VOLUME 97, ART. 3 PAGES 527-878

THE CERVIX

Consulting Editor

WARREN R. LANG

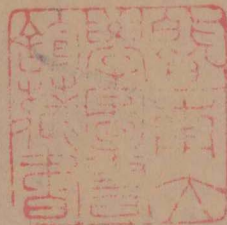
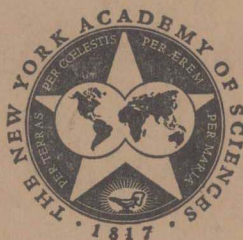
Warren R. Lang

AUTHORS

WARREN R. LANG AND ALFRED B. KUPFERBERG (*Conference Cochairmen*),
L. A. BALLARD, R. H. BARTER, C. T. BEECHAM, D. W. BOTTORFF, J. C. BUCK-
INGHAM, R. M. CALMAN, E. S. CARLIN, A. E. CLAIREAUX, M. R. COHEN,
N. COTTEN, D. N. DANFORTH, J. DAVIES, C. M. DOUGHERTY, R. H. FENNELL,
JR., F. FERNANDEZ, G. H. FLETCHER, A. G. FORAKER, C. A. FRICK, J. K.
FROST, C. F. GESCHICKTER, L. A. GRAY, T. H. GREEN, A. F. GUTTMACHER,
T. C. HALL, C. G. HARTMAN, Q. C. JAMES, E. KOTCHER, K. E. KRANTZ,
H. KUSAMA, W. R. LANG, A. F. LASH, G. LEGORRETA, G. C. LEWIS, JR., M. L.
MCCALL, D. MOHR, W. R. MOORE, L. PARSONS, S. F. PATTEN, JR., W. PATTON
PHILLIPS, J. H. M. PINKERTON, W. T. POMMERENKE, A. RAUZY, J. W. REAGAN,
G. S. RICHARDSON, E. M. ROBERTSON, M. ROLAND, A. RUBIN, F. RUTLEDGE,
R. B. SCOTT, R. SELDEN, A. J. SOBRERO, W. J. SWEENEY, G. TATARIAN, M.
TERRIS, H. ULFELDER, G. L. WIED, P. A. YOUNGE

Editor

MARY C. JOHNSTONE



NEW YORK

PUBLISHED BY THE ACADEMY

September 29, 1962

E705

879007

外文书库

3316

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

VOLUME 97, ART. 3 PAGES 527-878

September 29, 1962

Editor

MARY C. JOHNSTONE

THE CERVIX*

Conference Cochairmen

WARREN R. LANG AND ALFRED B. KUPFERBERG

Consulting Editor

WARREN R. LANG

CONTENTS

Introductory Remarks. By WARREN R. LANG..... 529

Part I. Fundamental Considerations

- Historical Aspects of the Cervix. By GABRIEL TATARIAN..... 530
 Developmental Aspects of the Human Cervix. By J. DAVIES AND H. KUSAMA..... 534
 Anatomy of the Human Uterine Cervix, Gross and Microscopic. By KERMIT E. KRANTZ
 AND W. PATTON PHILLIPS..... 551
 Cyclic Changes in the Endocervix of the Monkey and the Origin of the Cervical Mucus.
 By CARL G. HARTMAN..... 564
 Cervical Cell Inclusion Bodies and Viral Infections of the Cervix. By EMIL KOTCHER,
 LAMAN A. GRAY, QUINTON C. JAMES, CAROLYN A. FRICK, DORIS W. BOTTORFF.... 571

Part II. Physiology: Relation to Infertility

- Some Biochemical Aspects of the Cervical Secretions. By W. T. POMMERENKE..... 581
 Bacteriological Findings in the Mid-Cycle Endocervical Mucus in Infertile Women. By
 AQUILES J. SOBRERO..... 591
 The Fern Test in Menstrual Disorders and Infertility. By MAXWELL ROLAND..... 599
 The Sims-Huhner Test. By MELVIN R. COHEN..... 612
 Artificial Insemination. By ALAN F. GUTTMACHER..... 623

Part III. Benign Disease of the Nonpregnant Cervix

- Histochemistry of the Uterine Cervix: Normal Exocervical, Metaplastic, Dysplastic, In-
 traepithelial, and Invasive Squamous Carcinomatous Epithelium. By ALVAN G.
 FORAKER..... 632
 Epidermalization of the Cervix. By CHARLES F. GESCHICKTER AND FRANCESCA
 FERNANDEZ..... 638
 The Cervical Portio From Menarche On: A Colposcopic Study. By WARREN R. LANG. 653
 Dysplasia: A Basic Reaction to Injury in the Uterine Cervix. By JAMES W. REAGAN
 AND STANLEY F. PATTEN, JR..... 662

* This series of papers is the result of a conference entitled *The Cervix* held by The New York Academy of Sciences on December 7, 8, and 9, 1961.

美籍华人杨超吾先生

Histologic Diagnosis and Clinical Significance of Benign Lesions of the Nonpregnant Cervix. By CARY M. DOUGHERTY, WILLIAM R. MOORE, NADALYN COTTEN.....	683
Management of Benign Cervical Disease in the Cervix of the Nonpregnant Patient. By PAUL A. YOUNGE.....	703

Part IV. Cervix of Pregnancy

Topical Cytology of the Ectocervix in Pregnancy. By EDWIN M. ROBERTSON.....	714
The Healing of the Puerperal Cervix: A Bacteriological Study. By J. H. M. PINKERTON, R. M. CALMAN, A. E. CLAIREAUX.....	722
Connective Tissue Changes in the Cervix During Pregnancy and Labor. By JOHN C. BUCKINGHAM, RICHARD SELDEN, D. N. DANFORTH.....	733
Cervical Incompetence in Pregnancy. By ROBERT H. BARTER.....	743
The Incompetent Internal Os of the Cervix. By A. F. LASH.....	746
Management of Benign Lesions of the Cervix During Pregnancy. By ALAN RUBIN.....	755

Part V. Cervical Malignancy: Diagnosis and Evaluation

Cytology of Invasive Cervical Carcinoma and Carcinoma <i>in Situ</i> . By GEORGE L. WIED, GILDARDO LEGORRETA, DIETRICH MOHR, ANDRÉ RAUZY.....	759
Problems of Cervical Biopsy. By ROGER B. SCOTT AND LESTER A. BALLARD.....	767
The Histology of Carcinoma <i>in Situ</i> of the Cervix. By ROBERT H. FENNELL, JR.....	782
<i>Trichomonas vaginalis</i> and Cervical Epithelial Changes. By JOHN K. FROST.....	792
Pretherapy Evaluation in the Management of Cervical Cancer. By GEORGE C. LEWIS, JR.....	800
Epidemiology of Cervical Cancer. By MILTON TERRIS.....	808

Part VI. Cervical Malignancy: Therapy

The Management of Cervical Carcinoma <i>in Situ</i> . By CLAYTON T. BEECHAM AND ELWIN S. CARLIN.....	814
Radiation Therapy in Invasive Cervical Carcinoma. By FELIX RUTLEDGE AND GILBERT H. FLETCHER.....	821
Surgical Management of Invasive Carcinoma of the Cervix: Abdominal Approach. By LANGDON PARSONS.....	830
Surgical Management of Invasive Carcinoma of the Uterine Cervix: The Vaginal Approach. By MILTON L. MCCALL.....	835
Chemotherapy of Cervical Carcinoma. By GEORGE S. RICHARDSON, THOMAS C. HALL, THOMAS H. GREEN, HOWARD ULFELDER.....	841
Palliative Management of Carcinoma of the Cervix. By WILLIAM J. SWEENEY.....	870
Closing Remarks. By WARREN R. LANG.....	875

INTRODUCTORY REMARKS

Warren R. Lang

*Department of Obstetrics and Gynecology, The Jefferson Medical College
of Philadelphia, Philadelphia, Pa.*

This publication, it is hoped, fulfills a long-standing need for a re-review of old data on the uterine cervix and for a presentation of modern concepts and investigative problems. In organizing the conference on which this monograph is based, Alfred Kupferberg and I tried to pinpoint those areas where interest is most active and where thought, laboratory work, and clinical delving are most challenging.

The monograph is organized to consider six major aspects of the cervix: fundamental considerations; physiology, relationships to infertility; the benign pregnant cervix; the benign nonpregnant cervix; the diagnosis and evaluation of cervical malignancy; and, finally, the therapy of cervical malignancy. We have attempted therefore a complete coverage of contemporary viewpoints on the uterine cervix.

Except for a recent book by C. Frederic Fluhmann, *The Cervix Uteri and Its Diseases* (1961), there is no available publication dealing solely with this extremely important organ of the female.

There are, naturally, many areas of disagreement, as the reader will note in the papers comprising this publication. But then disagreement, even if only on a semantic basis, adds spice and ginger to all discussions.

Reference

FLUHMAN, C. F. 1961. *The Cervix Uteri and Its Diseases*. Saunders. Philadelphia, Pa.

Part I. Fundamental Considerations

HISTORICAL ASPECTS OF THE CERVIX

Gabriel Tatarian

The Jefferson Medical College of Philadelphia, Philadelphia, Pa.

It has been only in the recent past that the uterine cervix has achieved a degree of importance in medical literature. The earliest known medical records were those of the ancient Egyptians. That their knowledge of anatomy was very scant is attested by the hieroglyphic sign of the uterus—the bicornuate uterus of the cow. The *Papyrus Ebers*, dating back to the 16th century B.C. during the reign of Amenhotep I, discusses gynecological disorders in various passages. The external genitalia, the vagina, the cervix, and the uterus are named and differentiated. In the treatment for prolapse of the uterus, the cervix is described, and it is recommended that fumes of wax and charcoal be allowed to penetrate the uterine cavity.

About the 15th century B.C., the Sacred Vedas of the Hindus were written. Although the ancient Hindus permitted human dissection, their knowledge of anatomy was fanciful. The Sacred Code of Manu describes conception occurring during the menstrual epoch when the cervix opens “like the flowers of the water lily to the beams of the sun.” Hindu surgical technique was developed to a relatively high plane; many types of operations are described in their literature, as well as a variety of instruments among which are sounds, forceps, trocars, catheters, syringes, bougies, and rectal and vaginal specula.

The first references to gynecology by the ancient Greeks are found in the so-called Hippocratic collection. These works are the most ancient and complete treatises on gynecology and remained in vogue until the 16th century. Hippocrates and his disciples had little knowledge of anatomy or physiology. They based their theories on clinical observation and philosophical deductions. A great deal was written describing various uterine diseases: stenosis and rigidity of the cervix, cervical erosion and laceration, cancer, induration of the uterus, metritis, pyometritis, uterine displacement, leukorrhea, menometrorrhagia, and hematometra.

The outstanding figure among the ancient gynecologists was Soranus, who practiced in Rome during the 2nd century. The earliest scientific description of gynecological anatomy is found in his treatise *On the Nature of the Uterus and Female Pudenda*. Soranus describes the cervix:

“The os uteri lies in the center of the female genital organs, for the cervix is closed in by the labia; the os is removed from these, in some more, in some less, according to age; in adults, generally $3\frac{1}{2}$ or 4 inches; in those who have borne children, it comes to be nearer through elongation of the cervix. The size (of the os uteri) varies, and is in most persons normally as large as the outer end of the auditory meatus. It opens at certain times, as in the orgasm of coitus, to receive the semen, during menstruation that the blood may escape, in pregnancy according to the growth of the embryo, and in labour to the greatest extent until it will admit the full sized hand. In texture, it is soft and fleshy in

virgins, like the sponginess of the lungs or smoothness of the tongue; but in those who have borne, it becomes more callous, like the head of a polypus or, as Herophilus says, like the end of a bronchus—becoming hard through the passage of discharges and by parturition.”

Although he was not an obstetrician or gynecologist, Galen's (A.D. 130–200) monumental works were considered the supreme medical authority for centuries following Hippocrates. Indeed, it was he who dominated European medicine for nearly 14 centuries. In his voluminous works, Galen treats obstetrics and gynecology in a superficial manner. His account of the anatomy and physiology of the female genital organs was based on his dissections and studies in animals. In Galen's text, *On the Dissection of the Uterus*, we find this description of the cervix:

“The neck of the uterus consists of flesh (muscle) which is hard and cartilaginous, and becomes even harder in course of time, particularly in those who have conceived often and become aged. Herophilus compares this structure with the trachea. In the cervix is a foramen through which menstrual blood flows and through which the seed of the male passes. This opening varies considerably; it admits a fine probe, but when the uterus is gravid, nothing can pass through. During labor it opens again to its widest proportion. The position of the cervix also varies; it may be in midline, or it may be deviated to one side.”

The succeeding centuries, following the death of Galen, saw a marked decline in medical science and literature. As Christianity spread and rose in power, so progress in scientific medicine gradually declined. The Church prohibited human dissection and encouraged faith healing with miracles, prayers, charms, and amulets, while being antagonistic to scientific medicine. During the ensuing centuries little original work was done. Many writings were merely translations, compilations, or revisions of works by previous masters. Such were the texts of Oribasius, Aetius of Amida, and Paul of Aegina. Aetius stressed the importance of vaginal and bimanual examinations and the use of the vaginal speculum for examination and treatment of cervical ulcerations. With the ascendancy of the Moslems, about a century after the death of Paul of Aegina, very little progress was possible in gynecology. Because of their religious beliefs, Moslems were forbidden to perform pelvic examinations and gynecology was practiced only by a few women physicians and midwives. Arabic works on gynecology were chiefly translations from earlier Greek and Roman manuscripts.

During the Renaissance, the first noteworthy progress in gynecology was made by the anatomic studies, descriptions, and sketches of Leonardo da Vinci and Andreas Vesalius. Vesalius was said to be the first to break from the traditional concept of the bicornuate uterus and to describe the human uterus as consisting of one cavity.

Ambroise Paré, the French barber-surgeon and contemporary of Vesalius, was the first to recommend amputation of the diseased cervix. During the 16th century we see the emergence of scientific anatomy and the foundations of modern surgery. Important contributions to gynecological physiology were made during the 17th century, which has been termed the age of physiology. Notable contributions during this time were made by William Harvey, Marcello

Malpighi, Sanctorius (Santorio Santorio), John Mayow, Regnier de Graaf, Anton van Leeuwenhoek, and Thomas Willis. Considered founders of modern obstetrics and gynecology are François Mauriceau and Hendrik van Deventer. Of historical interest, in 18th-century England, are William Hunter and William Smellie who are considered among the great names of obstetrics and gynecology of their era.

The 19th century was to see scientific medicine and surgery revolutionized. The first radical operation for uterine cancer was performed in Germany in 1801 by Frederick Osiander by amputation of the carcinomatous vaginal portion. Konrad von Langenbeck is credited with performing the first vaginal hysterectomy for cancer in 1813. Rudolf Virchow's *Cellular Pathology* published in 1858 soon became recognized as the basis of scientific surgery. A prominent teacher and author during this time was Charles D. Meigs at the Jefferson Medical College, who published his work on acute and chronic diseases of the cervix. Later in the century, John Byrne of Brooklyn, treated cancer of the cervix by the use of electrocautery.

During the past 75 years, contributions and advances have been so extensive that time permits only the mention of a few highlights. In the areas of histology and pathology are the contributions of H. C. Coe, W. Cullen, R. Meyer, F. Kermanner, and E. Novak. In the area of early diagnosis of cervical malignancy are the contributions of W. Schiller's iodine test, G. N. Papanicolaou's exfoliative cytology, and H. Henselmann's colposcope. In the area of radiation therapy for cervical malignancy are the contributions by Y. L. Wickham, P. DeGraiss, C. W. Duval, R. Abbe, Henri Dominici, H. A. Kelly, K. V. Bailey, J. G. Clark, E. Zweifel, and H. L. Kottmeier. In the areas of surgical therapy for cervical malignancy are the contributions of E. Wertheim, F. Schauta, J. V. Meigs, and A. Brunschwig.

In summary, the cervix, which was once looked upon casually by the ancient physicians, now has attained an integral and vital role in the field of gynecology. The progress made in our understanding of the cervix and its diseases during the last 100 years far outweighs the contributions made in all previously recorded medical history. Attesting to the practical importance and value of these advances are the eminently superior results present day clinicians are attaining in their management of cervical disorders.

General References

- ALLBUTT, C. 1953. *Greek Medicine in Rome*. Macmillan. London.
- BOURNE, A. W. & L. A. W. WILLIAMS. 1953. *Recent Advances in Obstetrics and Gynecology*. Churchill. London.
- BREASTED, J. H. 1930. *The Edwin Smith Surgical Papyrus*. Univ. Chicago Press. Chicago, Ill.
- BRYAN, C. P. 1930. *The Papyrus Ebers*. Geoffrey Bles. London.
- CASTIGLIONI, A. 1944. *A History of Medicine*. Knopf. New York, N.Y.
- DANA, C. L. 1926. *Peaks of Medical History*. Hoeber. New York, N.Y.
- HEIDEL, W. A. 1941. *Hippocratic Medicine*. Columbia Univ. Press. New York, N.Y.
- HILTON-SIMPSON, M. W. 1922. *Arab Medicine and Surgery*. Oxford Univ. Press. London.
- KELLY, H. A. 1900. *Gynecology, its present, past and future*. Phila. Med. J. VI.
- LANGDON-DAVIES, J. 1927. *A Short History of Women*. Viking. New York, N.Y.
- LEONARDO, R. A. 1944. *History of Gynecology*. Freban. New York, N.Y.
- LIBBY, W. 1922. *The History of Medicine*. Houghton Mifflin Co. Boston, Mass.
- MEIGS, C. D. 1854. *A Treatise on Acute and Chronic Diseases of the Neck of the Uterus*. Blanchard & Lea. Philadelphia, Pa.

- NEUBURGER, M. 1925. History of Medicine. Oxford Univ. Press. London.
- RICCI, J. W. 1950. The Genealogy of Gynecology. Blakiston. New York, N.Y.
- ROBINSON, V. 1929. Pathfinders in Medicine. Medical Life Press. New York, N.Y.
- SCHILLER, W. 1933. Early diagnosis of carcinoma of the cervix. Surg. Gynecol. Obstet. **56**: 210.
- SINGER, C. 1925. The Evolution of Anatomy. Kegan Paul, Trench, Trubner and Co. London. 1925.
- THOMAS, H. 1935. Classical Contributions to Obstetrics and Gynecology. Thomas. Springfield, Ill.

DEVELOPMENTAL ASPECTS OF THE HUMAN CERVIX*

J. Davies and H. Kusama

Department of Anatomy, Washington University Medical School, St. Louis, Mo.

The high incidence of cervical carcinoma in women and the occurrence at the junction of the cervix and vagina of a zone of "epithelial instability" sensitive to estrogen have naturally aroused interest in the precise development of the parts involved. In the classical view^{1,2} the cervix and most of the vagina are Müllerian in origin, with the possibility that the lower end of the vagina may be derived from the epithelium of the urogenital sinus. In recent years there has been evidence that the human vagina is developed entirely from the urogenital sinus, the uterus and an indeterminate part of the cervix being of Müllerian origin.³ Variations in the development of the parts undoubtedly occur from one species to another and have been extensively reviewed in relation to the problem of their reactions to estrogenic stimulation.⁴ The occurrence of estrogenic effects in the genital tract of the newborn infant and in newborn animals has long been recognized;⁵ these effects have been termed by Courrier "la crise génitale du nouveau né."⁶ Extension of the cervical epithelium onto the vaginal aspect of the cervix, the so-called "physiological erosion" or "congenital ectropion" of Fischel,¹ is also well recognized. The so-called "squamous epithelial metaplasia" that takes place in the epithelium and glands of the cervix both spontaneously and in response to estrogen has also stimulated much speculation with respect to the problem of malignant change.⁷

The following original observations on the development of the human cervix have been made possible by the supply of human fetal material from the Department of Pathology, Washington University Medical School, and through the courtesy of Dr. Fritz Fuchs of the University of Copenhagen, Copenhagen, Denmark, to whom grateful acknowledgement is made.

Material and Methods

Human specimens were examined at the following stages: 6 weeks (18 mm.), 14 weeks, 17 weeks, 18 weeks, 22 weeks, 30 weeks, term, and 22 months (post-natal). The specimens were fixed in either Bouin's solution or Zenker-formol. In the larger specimens the vagina was opened to allow adequate fixation. The smaller specimens were sectioned sagittally in paraffin. The larger specimens were double-embedded in celloidin and paraffin over a period of several months and later sectioned sagittally on a sliding microtome. Staining was routine with hematoxylin and eosin. Staining with the periodic acid-Schiff (PAS) method and with mucicarmine was also carried out.

Observations

Summary of development of human uterus and vagina. The 2 Müllerian or paramesonephric ducts arise bilaterally as thickenings of the coelomic epithelium overlying the cranial end of the urogenital ridges in embryos of about 10

* The work described in this paper was supported in part by Grant A-4394 from the National Institute of Arthritis and Metabolic Diseases, Public Health Service, Bethesda, Md., and by a grant from the Josiah Macy, Jr. Foundation, New York, N.Y.

mm. (5½ weeks). The central area of the Müllerian thickening or plate then sinks in to form a funnel, the mouth of which remains open throughout life as the abdominal ostium of the Fallopian tube. The fimbriae develop around the ostium as proliferations of the surrounding coelomic epithelium and underlying mesoderm: accessory ostia are common. The caudal blunt extremity of the Müllerian funnel then grows caudally, descending in intimate apposition with the ventral wall of the Wolffian duct from which it may gain accessions of cellular material (FIGURE 2). The caudal growing tip of each Müllerian duct then

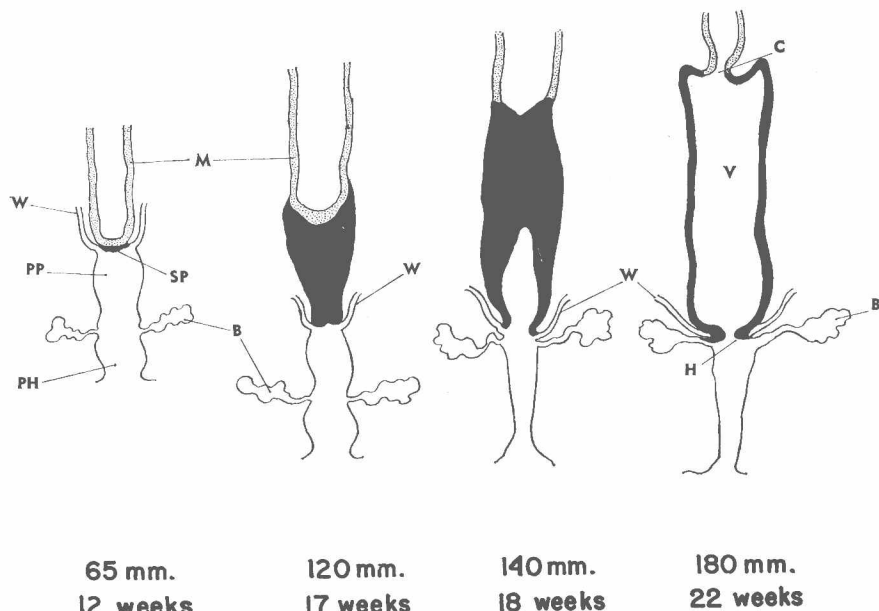
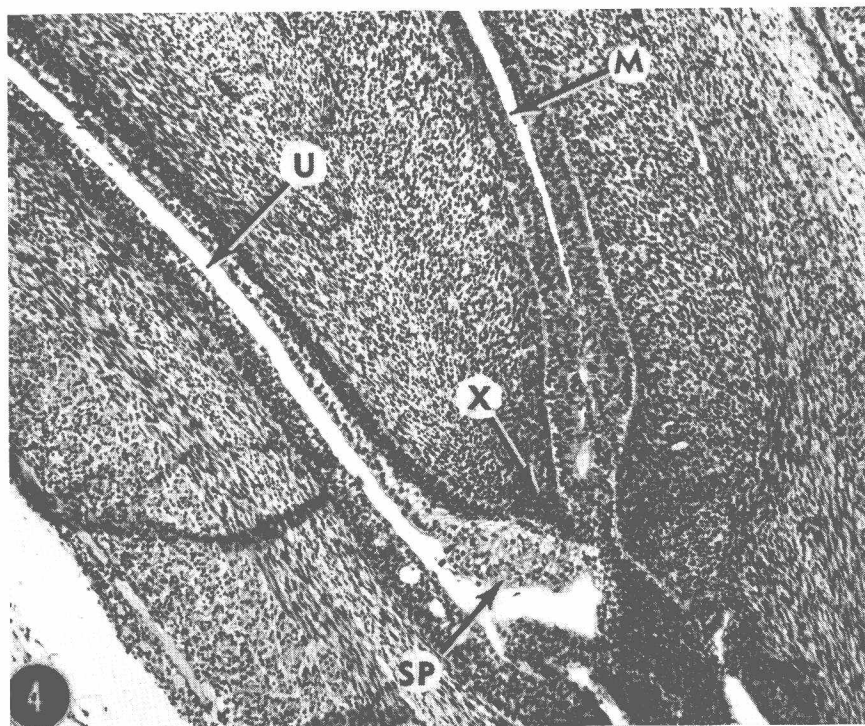
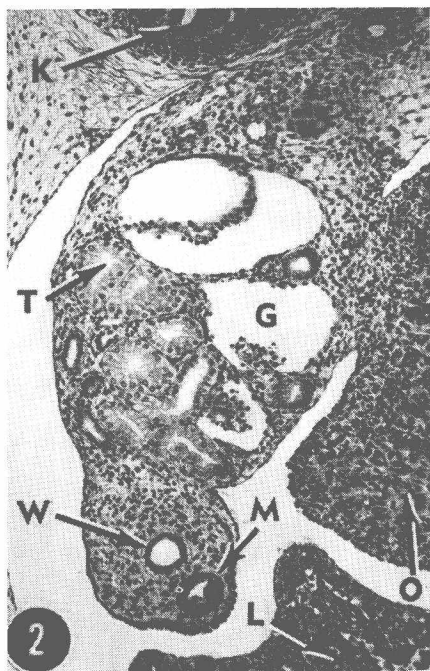


FIGURE 1. Schematic representation of the development of the human vagina and cervix uteri. The vagina is developed wholly or in major part from the epithelium ("sinus proliferation") in the posterior wall of the pars pelvina of the urogenital sinus. The corpus and cervix uteri are of Müllerian origin. (B) Bartholin's gland, (C) cervix, (H) hymen, (M) fused Müllerian ducts, (PH) pars phallica of urogenital sinus, (W) Wolffian duct, (V) vagina. Müllerian structures (mesodermal), stippled; sinus proliferation (endodermal), solid black. (Courtesy of D. V. Davies, Department of Anatomy, St. Thomas's Hospital Medical School, London.)

enters the unsplit mesoderm of the pelvic region in which the ducts are permitted to fuse. It seems inappropriate to continue the use of the term "utero-vaginal canal" to describe the fused Müllerian ducts in the region of the urogenital sinus, since the evidence is that the human vagina is entirely of urogenital sinus origin. The fused Müllerian ducts, the lumen of which remains double for a time, impinge on the posterior wall of the urogenital sinus at Müller's tubercle.

The modern view on the development of the human vagina and uterus is illustrated diagrammatically in FIGURE 1 and is based in part on the work of Bulmer.³ The illustration is largely self-explanatory, and space will not be taken to describe it in detail. The vagina is shown arising as a proliferation of



the epithelium in the posterior wall of the pars pelvina of the urogenital sinus and is, therefore, endodermal in origin. The pars pelvina of the sinus is the narrowed and elongated part distal to the bladder and is succeeded at the level of Bartholin's gland by the pars phallica of the sinus. The elongation of the sinus proliferation displaces the fused Müllerian ducts in a cranial and dorsal direction. The Wolffian ducts remain caught up in the sinus proliferations close to the pars pelvina and are later incorporated into the region of the hymen. Canalization of the solid sinus (vaginal) proliferation takes place between the 18th and 22nd weeks. The junction between the epithelium of the sinus proliferation and that of the fused Müllerian ducts probably lies in the approximate area of the cervix, a problem that will be considered later.

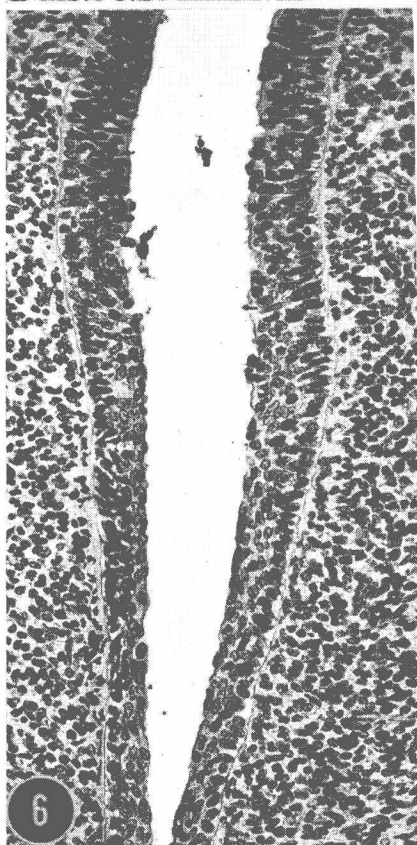
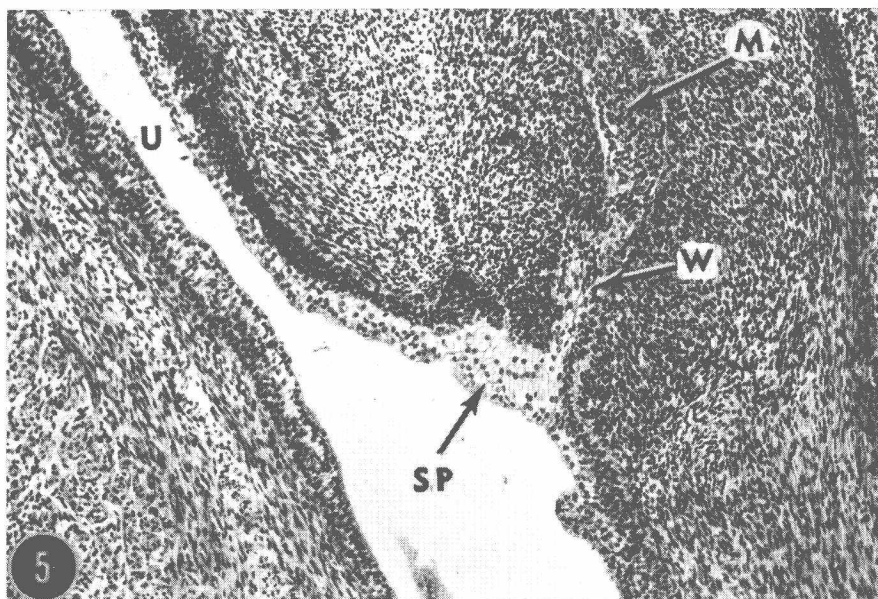
Details of the sinus proliferation and the nature of the epithelial structures involved are shown in FIGURES 3, 4, and 5. The sinus epithelium, from being a stratified epithelium of vacuolated cells at the 6th week (FIGURE 3), was 2-layered at the 14th week (FIGURE 4). At the latter stage it consisted of a deep layer of compact, deeply staining cells, several layers in thickness, and a superficial stratified layer of clear cells. Both layers are involved in the sinus proliferation, although it is the deep layer that actually fuses with the lower end of the fused Müllerian ducts. The basement membrane of the sinus epithelium could not be traced in perfect continuity with that of the Müllerian ducts but appeared to be deficient in the vicinity of the lower end of the Müllerian ducts (at **X** in FIGURE 4). This may be an artifact of tangential sectioning but may also represent the true situation. It is possible that there is a contribution at this point to the vaginal proliferation by the outlying mesoderm. The sinus proliferation extended dorsally to enclose the lower end of the fused Müllerian ducts in the form of winglike cellular masses on either side, as described by Bulmer³ and as shown in FIGURE 5.

The demarcation of the cervix from the vagina becomes established during the 5th month² by a massing of mesoderm around the lower end of the fused Müllerian ducts and by the formation of the vaginal fornices as proliferations of the stratified squamous epithelium.^{2,10} The junction between the Müllerian and the urogenital (vaginal) epithelium was tentatively identified in a fetus of 17 mm. (FIGURE 6) before the cervix was marked off from the vaginal canal. The now single canal of the fused Müllerian ducts was lined by a stratified columnar epithelium in which the nuclei were orientated at right angles to the

FIGURE 2. Section of ovary, mesonephros, and related parts of human embryo of 18 mm. (6 weeks). (G) glomerular cavity of mesonephros, (L) liver, (M) Müllerian duct, (O) ovary, (K) metanephros (kidney), (T) mesonephric tubule, (W) Wolffian duct. H. and E. $\times 100$.

FIGURE 3. Entrance of Wolffian duct into urogenital sinus of human embryo of 18 mm. (6 weeks). The Müllerian ducts have not yet fused or reached the sinus and so are not shown. The epithelium of the sinus is a stratified layer of clear cells which may be shown to contain glycogen and which rest on a distinct basement membrane. (U) urogenital sinus, (W) Wolffian duct. H. and E. $\times 100$.

FIGURE 4. Sagittal section of pelvic region of human fetus of 14 weeks. The Müllerian ducts are fused but still show separate lumina. Their blunt lower extremities lie in close relation to the posterior wall of the elongated pars pelvina of the urogenital sinus. The "sinus proliferation," made up of both layers of the urogenital sinus epithelium extends dorsally and cranially to enclose the Müllerian ducts (see FIGURE 1). The basement membrane of the sinus epithelium is interrupted at **X**, suggesting a contribution to the sinus proliferation by the cells of the surrounding mesoderm. (M) fused Müllerian ducts, (SP) sinus proliferation (anlage of vagina), (U) pars pelvina of urogenital sinus. H. and E. $\times 100$.



basement membrane. As the epithelium was traced in the direction of the vagina the nuclei became randomly arranged and predominantly orientated parallel to the basement membrane, forming a stratified squamous epithelium (FIGURE 6). The smooth muscle differentiating in the wall of the Müllerian canal extended caudally to a level slightly above the transition zone, being absent at the level of this zone: on this basis the transition zone was judged to lie at the site of the future cervix.

In the 22-week specimen the cervix was grossly demarcated from the vaginal vault but the details of the epithelial junction between the two parts were lost due to poor fixation. As far as could be determined the stratified squamous epithelium of the vagina extended deeply into the endocervical canal, ceasing abruptly about its mid-point. Smooth muscle was well differentiated in this specimen in the corpus uteri but was absent from the wall of the cervix, which contained a richly cellular mesoderm with many small vessels.

The striking stimulation of the vaginal epithelium at 22 weeks, presumably under the influence of estrogen, is illustrated in FIGURE 7. The deep proliferative layer of basophilic cells was conspicuous. The superficial layers of the epithelium were cornified and desquamating into the vaginal lumen which was almost obliterated.

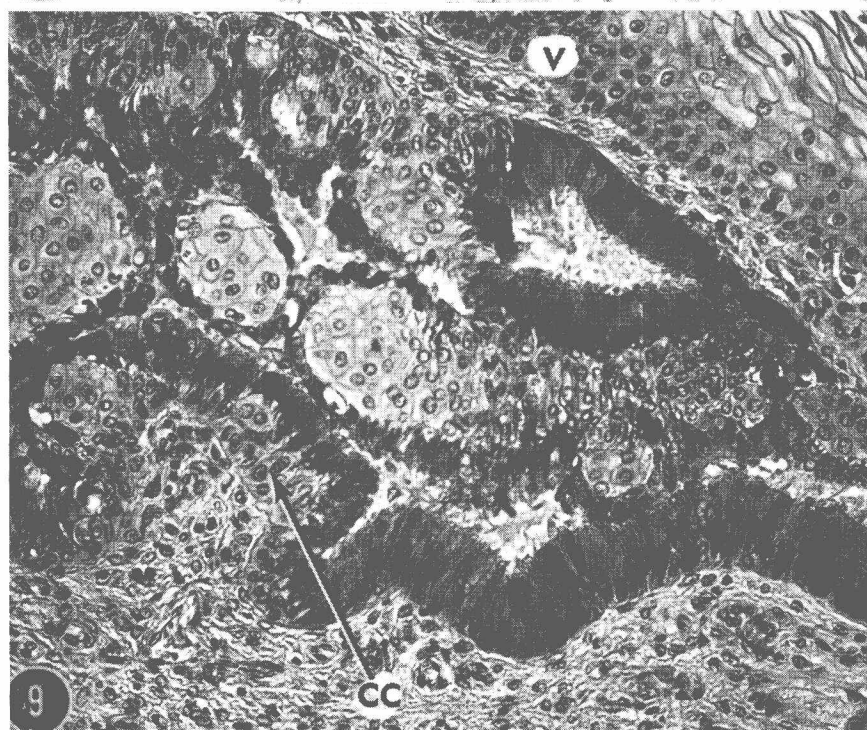
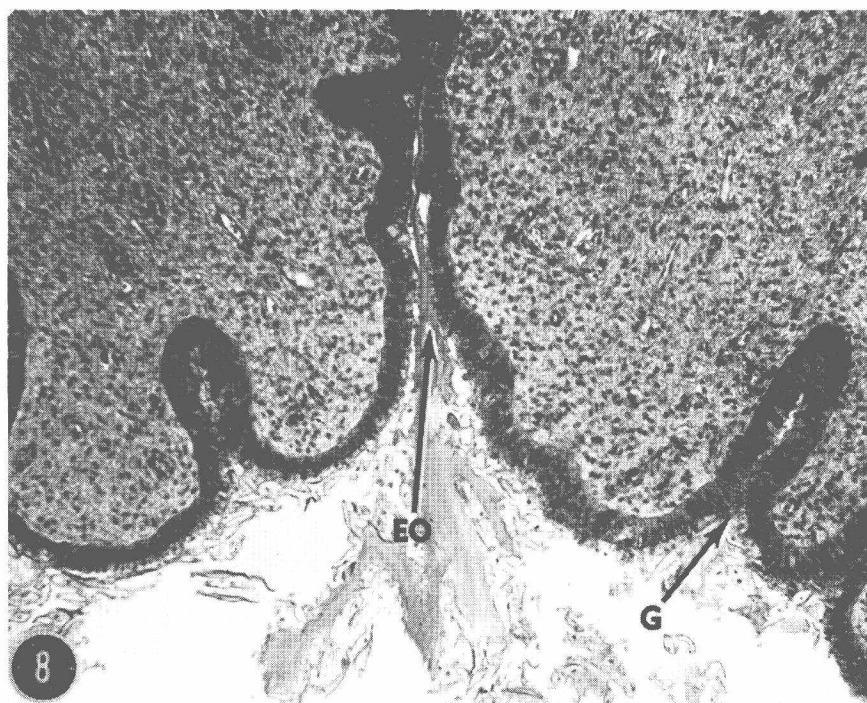
At 30 weeks the junction between the vagina and the cervix was excellently preserved (FIGURE 8). The junction between the stratified squamous epithelium of the vagina and the tall columnar epithelium of the cervix lay a considerable distance lateral to the external os, so that the so-called "congenital ectropion" already existed. The epithelium covering the vaginal aspect of the cervix was a relatively simple columnar or pseudostratified columnar one in which the cells were ballooned out at their luminal edges and distended with mucus. The epithelium of glands of the endocervix and of those which opened onto the vaginal surface of the cervix was more complex (FIGURE 9) and of two types. In most areas the epithelium was pseudostratified and heavily mucified, resting on the basement membrane. Elsewhere, chiefly in the fundus of the glands, the mucified columnar cells were separated from the basement membrane by several layers of clear cells. The nature of these clear cells will be discussed later. The absence of gonadotrophic effects in the ovary and the marked stimulation of the Fallopian tube in the 30-week fetus are shown in FIGURES 10 and 11.

At full term the cervix was strikingly hypertrophied and occupied two thirds

FIGURE 5. Sagittal section of the pelvic region from the same fetus as in FIGURE 4 (14 weeks). The clear cells of the sinus proliferation in the region of Müller's tubercle are prominent. The deep layer of basophilic cells of the sinus proliferation enclose the lower end of the fused Müllerian ducts as "winglike" extensions (*W*) on either side (see FIGURE 1). (*M*) Müllerian ducts, (*SP*) sinus proliferation, (*U*) pars pelvina of urogenital sinus, (*W*) winglike extension of sinus proliferation. H. and E. $\times 100$.

FIGURE 6. Longitudinal section through the junctional region between the vaginal (urogenital) epithelium and the cervical (?) or Müllerian epithelium. The latter is a pseudostratified columnar epithelium. As this Müllerian epithelium is traced inferiorly the nuclei change in orientation relative to the basement membrane, becoming characteristic of a stratified squamous epithelium in the vaginal region (lower part of the figure). This is from a 17-week human fetus. H. and E. $\times 220$.

FIGURE 7. Vaginal epithelium of human fetus of 22 weeks showing intense estrogenic stimulation. The basal proliferative layer of cells is basophilic. The superficial layers are cornified and undergoing desquamation. H. and E. $\times 100$.



of the total length of the uterus. The junction between the vaginal and cervical epithelium was very variable and depended upon the level of the section (FIGURE 12). In some areas the vaginal epithelium extended up to the edge of the external os; in others the junction lay far laterally in the direction of the vaginal fornices. Thus, the "congenital ectropion" at this stage could be envisaged grossly as an irregular island of cervical mucosa surrounding the external os with the margin of which it merged at numerous points, a situation that became apparent only by a study of serial sections. Details of the junctional zone are shown in FIGURE 13. The epithelium of the vagina was a thick stratified squamous one, the superficial cells of which were heavily cornified and desquamating into the vaginal lumen. The deep layer of the vaginal epithelium consisted of several rows of deeply basophilic cells in which mitoses were common: this was the proliferative layer. The intermediate layer consisted of clear cells with distinct cell membranes, strongly picked out by the periodic acid-Schiff method and which also contained a small amount of intracellular glycogen. At the transition zone (X in FIGURE 13) the basal layer of the vaginal epithelium disappeared abruptly and the intermediate layer became continuous with the cervical epithelium. The cervical epithelium appeared to be a stratified or pseudostratified columnar epithelium the superficial layers of which were irregularly mucified. At first sight the cervical epithelium beyond the junctional zone (FIGURE 13) might pass as an example of "stratified squamous metaplasia." However, a careful study of the cells in this region showed that they are in reality quite unlike those of the vaginal epithelium in that they lack the basal proliferative layer of basophilic cells and the nuclei are orientated in general at right angles to the basement membrane. Desquamated cornified and degenerating cells clung to the surface of the cervical epithelium (FIGURES 13 and 14), suggesting that it might have been cornified at an earlier stage. The stroma of the cervix was highly vascular and densely infiltrated with leukocytes of the lymphocytic type (FIGURE 14). Many leukocytes could be observed migrating through the cervical epithelium. Leukocytes were not observed within the stratified squamous epithelium of the vagina. The cervical stroma was composed of a loose and very cellular connective tissue without smooth muscle. There were many large blood vessels some of which were intimately applied to the cervical mucosa, ballooning it out into the vaginal vault as polyp-like structures over which the epithelium was very attenuated. Bleeding from such areas would seem to be very likely and a more likely source in the newborn child than the endometrium.

FIGURE 8. Region of the external os of the cervix of a human fetus of 30 weeks. The epithelium, which was thick and cornified, faded out abruptly just beyond the edge of the illustration. The epithelium over the vaginal aspect of the cervix is columnar or pseudostratified with moderate mucification. Glands open on to the vaginal surface of the cervix as well as into the cervical canal. The epithelium of these glands is thicker than on the free surface of the cervix. (EO) external os, (G) gland. H. and E. $\times 100$.

FIGURE 9. High-power view of one of the endocervical glands from the same specimen as in FIGURE 8 (30 weeks). The lining epithelium is a tall, pseudostratified, columnar epithelium, intensely mucified but with modifications in the fundus of the glands. In the latter the epithelium is thickened and the basal layer of the epithelium consists of clear, nonmucified cells, the nuclei of which are arranged predominantly at right angles to the basement membrane and so are more typical of a columnar epithelium than of a stratified squamous epithelium. The apical cells of this modified epithelial zone of the glands are mucified. (CC) clear cells, (V) vagina. H. and E. $\times 220$.

