F. A. Langley · A. C. Crompton

Epithelial Abnormalities of the Cervix Uteri

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F. A. Langley, M.Sc., M.D., F.R.C.Path., F.R.C.O.G.,
Professor of Obstetrical and Gynaecological Pathology, University of Manchester.
Consultant Pathologist, St. Mary's Hospital for Women and Children, Manchester

A. C. Crompton, M.D., F.R.C.S.Ed., M.R.C.O.G.,
Consultant Obstetrician and Gynaecologist, Leeds (St. James's) University Hospital.
Sometime Lecturer in Obstetrics and Gynaecology, University of Manchester

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Introduction

The introduction of colposcopy and exfoliative cytology as a means of examining the cervix uteri has opened up the possibility of studying the preceding and early stages of invasive carcinoma of the cervix and has also brought to light a number of conditions which are possibly only indirectly related, if related at all, to cervical neoplasia. Using these methods combined with histological evaluation it is possible to gain some insight into the natural history of cervical carcinoma. The importance of this is not confined to the cervix for, in this respect, the cervical lesions may prove a paradigm for those of the bladder, stomach and elsewhere.

At present the broad outline of the natural history of these cervical lesions is emerging but the temporal and spatial relationships of the various phases is unclear, largely because of the number of possibilities envisaged which involves more variables than can be controlled in any one investigation. In this monograph we have endeavoured to indicate the limitations of the various approaches and to stress the need for controlling the accuracy of assessment whether it be histological, cytological or colposcopic.

It is well sometimes to sit back and view a disease as a biological experiment in order to improve our understanding of its evolution and thereby gain some insight into its possible control. This has been our aim in this monograph rather than to present a comprehensive account of the present state of our knowledge of cervical abnormalities which would be both tedious and disjointed.

We have only lightly touched on treatment and we have avoided discussing the value of mass screening, rather presenting the abnormalities in broad biological terms. For it seems to us that these lesions are probably multifactorial in origin and that a variety of factors outside the immediate control of the gynaecologist may affect the patterns of these lesions in the future, especially changing customs of marriage and sexual mores.

We would like to thank Professor W. I. C. MORRIS for the facilities of the Department of Obstetrics and Gynaecology, Manchester University, which have made this study possible. We are grateful to Mr. B. FIGG for preparing the photomicrographs and Dr. OLLERENSHAW, together with his staff in the Department of Medical Illustration, United Manchester Hospitals, for drawing the diagrams. The editor of the Journal of Clinical Pathology has kindly given us permission to reproduce Figs. 2.1., 3.13., 3.14. and 3.15., and the editor of the Journal of Obstetrics and Gynaecology of the British Commonwealth has courteously allowed us to include Figs. 3.9., 3.10. and 3.11. Those of our colleagues who from time to time have read portions of the text whilst it was in preparation have rendered us a valuable service in their critical and constructive comments. Finally we would thank Mrs. D. SHAW and Miss S. HAMILTON and Miss A. GODSELL for typing drafts of various chapters and Mrs. J. EDWARDS for the typing of the completed manuscript.

F. A. LANGLEY, A. C. CROMPTON, 1973.

Chapter 1

The Normal Cervix

The cervix uteri is covered by two types of epithelium, the portio vaginalis by stratified squamous epithelium and the endocervix by columnar epithelium. The purpose of this chapter is to examine the normal structure and function of these two epithelia in broad biological terms as a background to a consideration of their pathology.

1. The Development of the Cervix Uteri

The development of the cervix has been extensively reviewed by HORSTMANN and STEGNER (1966) and modern views are discussed by DAVIES and KUSAMA (1962). In the classical view, the cervix and the upper part of the vagina are Müllerian in

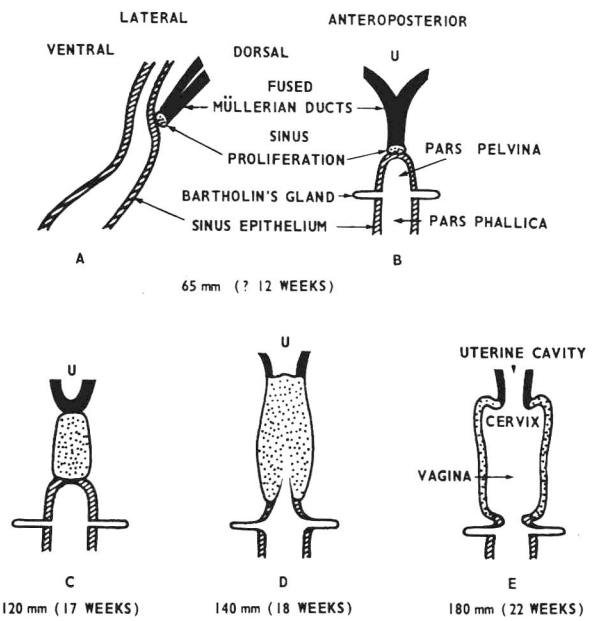

Fig. 1.1. A schematic representation of the development of the human vagina and cervix, after BULMER (1957) and DAVIES and KUSAMA (1962). The area shaded black represents the fused Müllerian ducts; the stippled area is the sinus proliferation and the cross hatched area is the epithelium of the urogenital sinus

origin whilst the lower end of the vagina is developed from the urogenital sinus (KOFF 1933). BULMER (1957) has brought forward 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. He has shown that the vagina arises as a proliferation of the epithelium in the posterior wall of the pars pelvina of the urogenital sinus and is therefore endodermal. The pars pelvina of the sinus is the narrowed and elongated part, distal to the bladder, which is succeeded at the level of

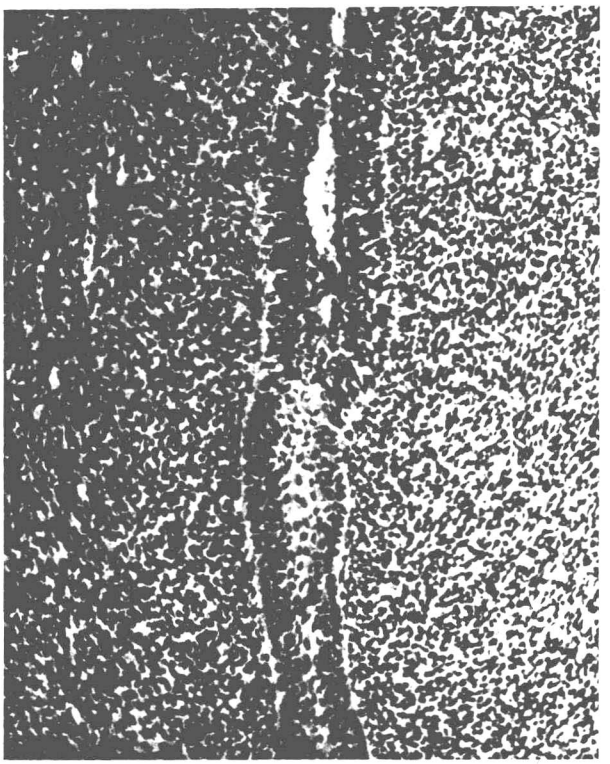

Fig. 1.2. In the upper part of the field the fused Müllerian ducts are developing a cavity, later to form the lumen of the uterus. In the lower part of the field is the solid core of epithelial cells formed from the sinus proliferation. From a fifteen-week foetus. (H. & E. ×120)

Bartholin's gland by the pars phallica of the sinus. The proliferation forms a solid cord of cells which displaces the Müllerian ducts cranially and dorsally. The vagina is formed by canalization of this cord between the eighteenth and twenty-second week of gestation. The junction between the epithelium of the sinus proliferation and the fused Müllerian ducts probably lies in the region of the cervix. The demarcation of the cervix from the vagina is established during the fifth month by massing of mesoderm round the lower end of the fused Müllerian ducts and the formation of the vaginal fornices as proliferations of the stratified squamous epithelium. The sequence of changes is shown in Figs. 1.1., 1.2. and 1.3.

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DAVIES and KUSAMA (1962) have shown that at thirty weeks the junction between the vaginal and cervical epithelium is well defined (Fig. 1.4.) but variable in site. In some areas the squamous epithelium extends up to the level of the external os but in other areas of the same cervix the junction between squamous and columnar epithelium lies far out laterally in the vaginal fornix. At the junction the basal layer of the vaginal epithelium may disappear abruptly and the intermediate layer become continuous with the cervical epithelium. The cervical epithelium at this junctional

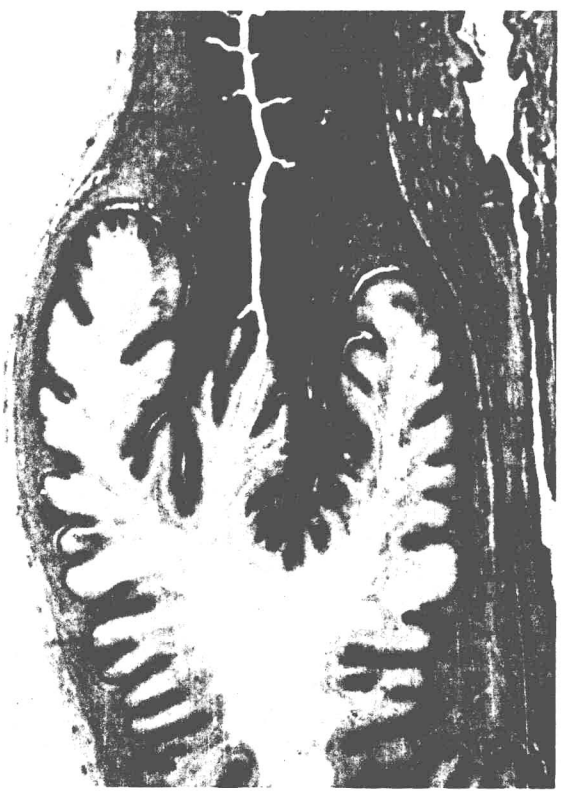


Fig. 1.3. A section from a twenty-seven week foetus. The vagina and fornices are now well formed. (H. & E. ×8)

zone is of stratified, or pseudostratified, columnar type. They consider it to differ from squamous metaplastic epithelium in that the nuclei of the basal layers are arranged at right angles to the basement membrane. GRUENAGEL (1957), MATĚJKA (1963) and HORSTMANN and STEGNER (1966) regard these subcylindrical cells as "reserve cells", corresponding to the reserve cells described by HOWARD *et al.* (1949, 1951) in older women. According to GRUENAGEL there are no intercellular bridges between these reserve cells, the cytoplasm stains lightly, the nuclei are round and vesicular. The cytoplasm of many of the cells gives an alcian blue positive reaction which may indicate a relationship to the columnar cells.

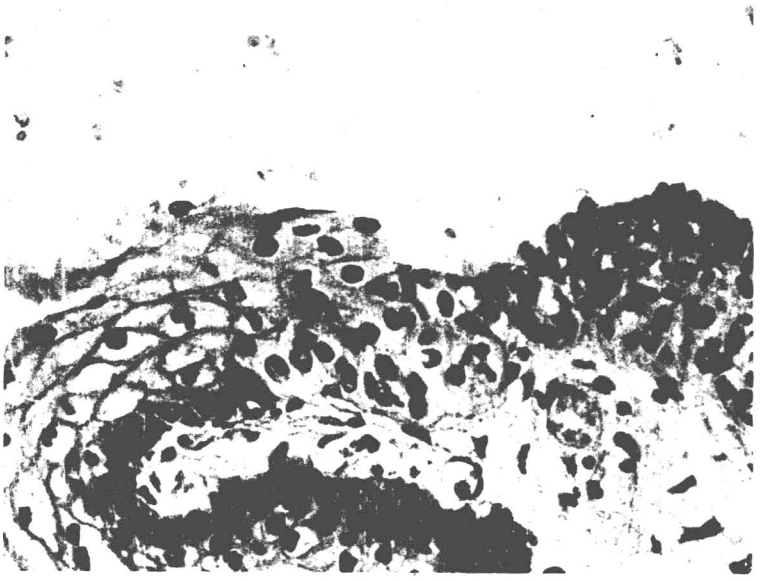


Fig. 1.4. A section from the squamo-columnar junction of a thirty-week foetus. The cells of the basal and parabasal layer stop abruptly but those of the intermediate layer are continued beneath the columnar layer of the endocervix. (H. & E. ×300)

In late foetal and early neonatal life the squamous epithelium of the vagina and cervix is very thick but it is rapidly shed in the first few weeks after birth. This change is probably caused by the fall in circulating hormones derived from the mother, and in particular by the fall in oestrogen level. The complex pattern of the endocervical epithelium in late foetal and early neonatal life in many ways resembles that seen in cervical polypi resulting from the use of oral contraceptives and is a reminder that the effects of both oestrogen and progesterone must be considered.

2. The Squamous Epithelium of the Cervix

a) The Histological Pattern

The preceding discussion emphasises that a close relationship exists between the squamous epithelium of the vagina and the cervix while the differences, as in the response to hormonal stimuli, are usually only ones of degree. Although this squamous epithelium is endodermal in origin it will also be profitable in our subsequent discussions to compare it with that of the epidermis.

The squamous epithelium of the vagina and cervix is not usually keratinized. Indeed the keratinization of vulvar epithelium sharply distinguishes it from vaginal epithelium at the vulvo-vaginal junction. Nevertheless in uterine prolapse and certain pathological states the cervico-vaginal epithelium may keratinize. Dierks (1927) originally described five zones or layers of cells in this epithelium. This system is usually followed for descriptive purposes, although with some variation in terminology according to the author. As Krantz and Phillips (1962) point out it is not

usually possible to recognize all the layers in every specimen. Table 1.1. summarizes some of the terms used.

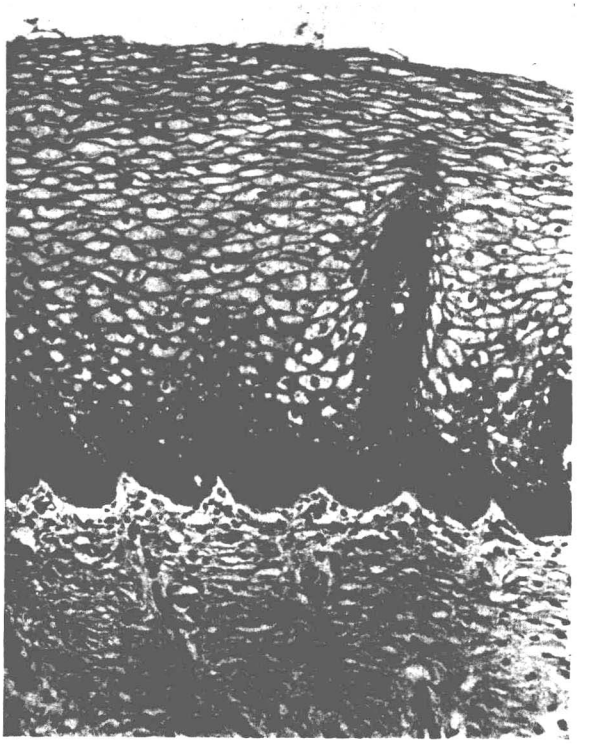
The *stratum basale* (stratum cylindricum) is a single row of small cubical cells with large, dark-staining nuclei and a high nucleo-cytoplasmic ratio. The *stratum spinosum profundum* is also known as the prickle-cell or parabasal layer. It consists of a varying number of layers of polyhedral cells with large dark-staining nuclei. Normally mitotic figures may sometimes be seen in this stratum as in the stratum basale. In the

Table 1.1. The layers of the squamous epithelium of the cervix uteri

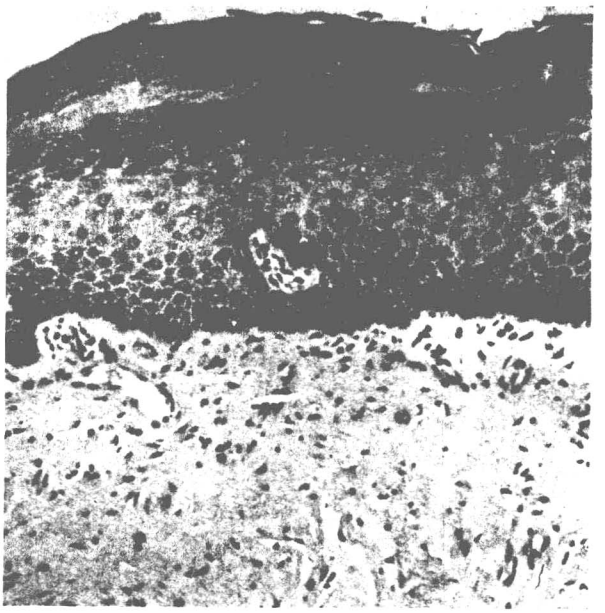
Terms used in the text	Synonyms	
Stratum basale	Stratum cylindricum	Stratum germinativum (HACKEMANN *et al.*)
Stratum spinosum profundum parabasal layer	Dark Zone (TRAUT *et al.*)	Stratum spinosum (HACKEMANN *et. al.*)
Stratum spinosum superficiale, intermediate layer	Light Zone (TRAUT *et al.*)	
Intraepithelial zone stratum granulosum	Verdichtungszone (STEMSHORN)	Stratum functionalis (HACKEMANN *et. al.*)
Stratum superficiale	Verhornungszone (DIERKS)	
	Stratum corneum (PAPANICOLAOU)	
	Stratum functionalis (DIERKS)	

stratum spinosum superficiale the cells tend to be flattened. The cytoplasm of the cells contains glycogen and may be vacuolated and the nuclei stain less darkly than in the deeper layers and are vesicular. Mitoses are rarely, if ever, seen. This zone is sometimes known as the intermediate, navicular or clear-cell layer (KRANTZ and PHILLIPS 1962). HORSTMANN and STEGNER (1966) term the whole stratum spinosum the *Intermediarzone*, whilst DIERKS (1927) terms all the first three zones the *stratum basalis*. Between these three layers and the superficial layer lies a narrow, inconstant zone, the intraepithelial or condensation zone. It consists of closely packed, flattened cells in which both the nuclei and cytoplasm tend to stain darkly and if the superficial zone is keratinized keratohyaline granules are seen, the layer is then termed the *stratum granulosum*. The fifth and outermost layer is the *stratum superficiale*. This consists of several layers of flat, elongated cells, with pyknotic nuclei but if keratinization occurs nuclei will be absent. PAPANICOLAOU *et al.* (1948) distinguish two types of superficial layer — cornified and keratinized. The use of these two terms has caused some confusion, which has been discussed at length in Acta Cytologica 4, (1960). The terms are not strictly synonymous since they describe differing appearances of this outer layer (see Fig. 1.5.).

From this brief description of the layers of the squamous epithelium of the portio vaginalis it will be seen that the terminology used varies with the author and is not conducive to the maximum degree of clarity. Moreover, the boundary between the layers is often not sharply defined, particularly between the stratum spinosum profundum and the stratum spinosum superficiale. HACKEMANN *et al.* (1968) found that the electron microscope failed to reveal five clear-cut succesive layers and proposed to speak of a basal layer or stratum germinativum, a wide stratum spinosum and a superficial multilayered stratum functionalis.



a



b

Fig. 1.5. a Typical cornified squamous epithelium of the ectocervix. The basal (germinative) layer is well defined, the other layers gradually merge into each other, b Keratinized epithelium of the ectocervix. The granular, or intraepithelial, zone is well defined. (H. & E. ×120)

The pattern of cervical squamous epithelium varies from epoch to epoch of a woman's life and at any period it may vary from place to place in the same cervix. At birth the squamous epithelium of the cervix is very thick and has a basket-weave

Fig. 1.6. The squamous epithelium of the ectocervix and vagina of a newborn infant. The epithelium is thick and the superficial layers are exfoliating. (H. & E. ×50)

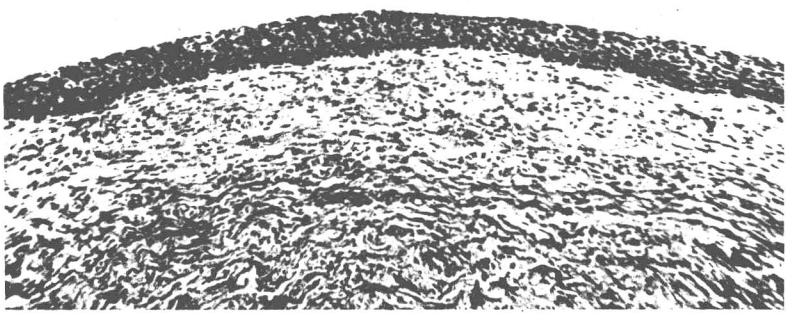


Fig. 1.7. Atrophic squamous epithelium from the ectocervix. Note the loss of stratification but the relative cellularity. From a woman of sixty-one years whose menopause was eleven years previously. (H. & E. × 125)

structure (Fig. 1.6.) presumably as a result of oestrogenic stimulation. The greater part of this epithelium exfoliates as the oestrogenic effect is lost and it is remodelled as a thin menbrane. After the menopause the squamous epithelium becomes atrophic (Fig. 1.7.); it is thin, stratification is reduced or almost lost, the nuclei are dark and the cytoplasm of the cells is scanty and hence they are more closely packed together. The rate of atrophy varies considerably from woman to woman. In some, atrophy occurs soon after the cessation of menstruation but in others there may be very little atrophy even ten years after the menopause. The cause of these differences is uncertain, it may depend on differences in steroid hormone production by extragenital sources or on differences in sexual activity.

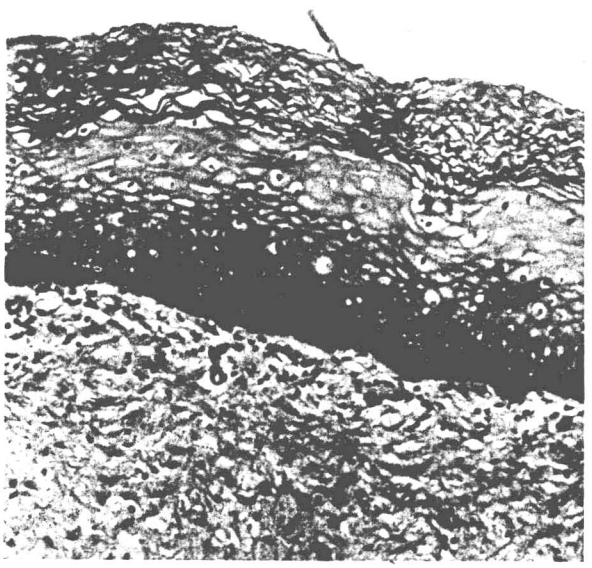


Fig. 1.8. Squamous epithelium showing a "basket-weave" arrangement of the cells of the superficial layer. (H. & E. × 120)

During the childbearing period the squamous epithelium of the portio vaginalis of the cervix is not static but varies with the phase of the menstrual cycle, in pregnancy and during the puerperium. Normally during this epoch the squamous epithelium is well glycogenated in the upper layers but patches of glycogenated epithelium may sometimes be seen sitting next to non-glycogenated epithelium. Often the cells in the more superficial layers are loosely attached to the underlying cells giving a basket-weave pattern (Fig. 1.8.) and patches of such epithelium may be interspersed with more compact epithelium. The contour of the epithelial-connective tissue junction varies; sometimes it is straight and flat but often wavy. This waviness is determined by the underlying vascular pattern and is usually associated with squamous metaplasia but sometimes it persists far out on the portio vaginalis reaching almost to the fornix and in such a site it is unlikely always to be the result of prior squamous metaplasia.

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