EARLY HISTOLOGICAL DIAGNOSIS OF CERVICAL CANCER

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Editor's Foreword

Here in elaborate detail is published one of the most vivid descriptions of the entire oncologic spectrum of histopathological entities found on the cervix. The lucidity of presentation carries the reader from the normal squamous pattern through the maze of intermediate disorders all the way to overt invasive carcinoma. The important discipline that this material deals with is clarified for both the clinician and the pathologist in a manner that melds pathogenetic theory, microscopic histomorphology, and practical clinical application.

The book addresses itself to a series of gynecological problems that have been designated collectively as a "no-man's land" in the sense that they have heretofore been rather poorly understood and inconsistently managed. Few tissues undergo the panorama of changes that are possible on the cervix. Since this "Pandora's box" was first opened by Schiller in 1928 with his description of intraepithelial carcinoma of the cervix, a whole panoply of preinvasive and early invasive pictures has been recognized.

Introduction of cytological screening techniques provided the impetus needed for codification of the subtle changes that occur on the cervix. With the identification of large numbers of lesions of dubious nature, lying somewhere between clearly normal and malignantly invasive, it became essential in terms of prognostic potential to determine their real significance by scientific means. Obviously, this could not be accomplished until it was possible to identify such growth variants by consistently applicable criteria. This accomplished, the natural life history of the evolution of cervical dysplasia to clinical carcinoma is revealed. Moreover, concepts concerning carcinogenesis are derived and programs of management created.

Many important questions are raised and answered here. Doctor Burghardt assails areas that others before him have avoided. He sheds light into dark corners, elucidating issues of great importance by bringing logic and objectively substantive evidence to bear. The reader's attention is especially directed to two unique features of this volume. First, we are presented with an extensive survey of data on site preferences to help in identifying lesions and, equally important, in understanding how various lesions relate to each other. This material does not appear anywhere else in monographic form. Second are the exceptionally fine overview photographs that afford such unusually clear histopathological details covering relatively broad expanses of cervical epithelium. The process by which they are obtained is explained in the text. Their special attributes become immediately apparent to the reader in terms of the degree of understanding and clarification they give. Doctor Burghardt makes it clear that the technique for obtaining such encompassing sections is available to all regardless of the constraints, imposed by limited laboratory facilities. The importance of this technical advance cannot be overemphasized as it provides practical and critically definitive diagnoses of these disorders.

Emanuel A. Friedman

Foreword

In this monograph my longtime coworker, Erich Burghardt, presents to the scientific community the results of his investigations into the area of early histological diagnosis of cervical carcinoma. The subject had its origins here in Graz in the classic contributions of Schauenstein in 1908. With the introduction of Schiller's iodine test, colposcopy and cytodiagnosis, the problem has enjoyed worldwide discussion, both from the morphologic and the clinical points of view. It is recognized that, heretofore, it has not been possible to achieve complete agreement on all relevant issues. This situation is particularly regrettable because the clinical management of the epithelial changes described by Burghardt must of necessity be based on clear-cut, definitive histological diagnoses. One may justfiably assume that Burghardt's accomplishments will contribute considerably to the clarification of the various unresolved histological lesions and the clinical problems to which they relate.

All the histological patterns that can be observed on the portio, from normal squamous epithelium to early invasive carcinoma and microinvasive adenocarcinoma, are discussed in great detail with regard to their clinical evaluation. They are illustrated in uniformly impressive histological pictures. Burghardt takes into consideration the world literature and expounds on his unique concepts based on the results of careful and exact observations.

The importance of this subject leads me to express the hope that both histopathologists and gynecologists concerned with the early diagnosis and treatment of cervical cancer will accord this well-conceived, classical and precedent-setting monograph the interest it merits.

Ernst Navratil

Preface

This book owes its existence to the central role that early diagnosis and treatment of cervical carcinoma played during my training and period of activity under Professor Navratil, Chairman of the Universitäts-Frauenklinik in Graz. After he took over the clinic in 1946, Professor Navratil provided all the prerequisites for a successful program for early cancer detection. He was one of the first (the first in Austria) to introduce Papanicolaou cytodiagnosis. Colposcopy became a routine examination in his clinic. He quickly recognized the importance of serial sections of large cervical biopsy specimens. These techniques were systematically improved until they could offer selective therapy for early stages of cervical carcinoma.

The early histological diagnosis of cervical cancer thus became closely allied with the clinic. A large case load provided new diagnostics problems as well as the opportunity to study all the aspects of the genesis of cervical cancer. I had the good fortune to become associated with these developments in 1954. It is unnecessary to emphasize how important it was to learn to recognize the specific lesions not only from the histological point of view but also from the vantages of cytology, colposcopy and therapy. In this regard and for his constant support of my activities I shall always be indebted to Professor Navratil.

My thanks are also due to those teachers who made the first steps in pathological anatomy and histology possible — the late Professor Th. Konschegg, Chairman of the Pathologisch-Anatomischen Institutes of the Universität Graz, and his successor, Professor M. Ratzenhofer. Professor Ratzenhofer showed constant interest in my histological activities even after I had left his institute and he was always prepared to advise me or to discuss new problems.

My friend, Fritz Bajardi, deserves not to be mentioned last, for he was my long-time companion first at the pathology institute and later as assistant in the Frauenklinik. We discussed nearly every subject covered herein. These discussions contributed much to the evolution of this book. It was Bajardi who first recognized the regularity of epithelial borders based on study of the bronchial mucosa. The reader cannot fail to appreciate the significance of this observation.

Finally, I want to thank the Georg Thieme Verlag, and especially Dr. h. c. Günther Hauff, for their willingness to publish this book in its present form. I am also thankful to the publisher's staff for their friendly assistance in helping me realize this work.

Erich Burghardt

Contents

Chapter One

Introduction

Only he who has completely familiarized himself with the growth processes of carcinomas can apply himself successfully to the study of their genesis.
H. Ribbert

Two stages are involved in early diagnosis of cervical carcinoma: screening and biopsy. The earliest suspicion of the presence or the development of a malignant change may be confirmed by means of screening techniques. These include *Schiller's iodine test, Hinselmann's colposcopy, Papanicolaou's cytodiagnostic approach,* and *colpomicroscopy* by the method of Antoine and Grünberger. As the next step sites of recognizable or suspected lesions on the cervix are subjected to biopsy and histological examination. These will provide either preliminary information or final diagnosis according to the extent of the biopsy and the depth of histological study of the material submitted. In either case further medical management will be determined by the findings. Hence, the attendant physician expects to receive information from which he may draw unequivocal conclusions. The overworked histodiagnostician, by contrast, sees himself confronted with a vast variety of pathological pictures and must decide if any are to be considered carcinoma or are somehow related to cancer. Such decisions may be made easily whenever they involve completely developed and clear-cut changes. If unclear, however, histological patterns may not lend themselves to meaningful conclusions, often giving rise to doubtful situations. Interpretation of these can easily become a matter of personal conviction. Disappointments arise as a result of the discrepancies between the expectations of the clinician and the histologist's uncertain or even subjective answers to his questions. These are especially reflected in the results of early diagnostic efforts. The histodiagnostician gets the brunt of the complaints concerning prevailing inability to obtain even approximate concurrence in results from one diagnostic center to another. Whether or not these complaints are justified is another matter. Nevertheless, the imperfect understanding between clinician and histologist soon changes the clinician's attitude of enthusiasm to one of resignation.

It is quite conceivable that cytological diagnosis has also become a source of similar misunderstanding, perhaps more so in Europe than in the United States. The technique was taken over by the clinician almost from the beginning. To date it has remained rather exclusively in his control. As a consequence, the cytologist with little or no prior histological training has perforce been required to gain insights into matters that were previously inaccessible to him. Thus his expectation that the finding of atypical cells in the vaginal smear demanded clarifying histological diagnosis was firmly based and not merely the result of statistical considerations. Expected clarification may not always have been forthcoming, particularly if the histologist was unwilling to "overvalue" epithelial changes or if, in his view, the diagnosis of carcinoma in situ should not be established. In the course of time the role of the cytodiagnostician was thus reduced to absurdity.

The objective of this book is to review the problems encountered in the early histological diagnosis of cervical cancer not only for the histologist but also for the interested clinician

and the practicing gynecologist. A number of very typical illustrations should elucidate the microscopic aspects of those changes which we repeatedly encounter in the framework of early diagnostic efforts or which merit our special attention, since they relate to the very matrix on which cervical carcinoma occurs.

With very few exceptions, the illustrations consist of serial step-sections of routinely evaluated conization slides (see p. 363 ff.). They were selected from a much larger number of pictures made in connection with the study of about 1500 cases. The advantage of using photographs of such material is that the patterns can be selected on the basis of surveyable relationships; thus deceptive conclusions which might have resulted from reproducing sections that could not be studied extensively were assiduously avoided.

Many of the pictures show multiple exposures. This technique makes it possible to assemble on one illustration various desired sections from the histological sample. It also avoids the disadvantage of being left with small sections of the overall picture when studying patterns at considerable magnification. Photographs produced by the method we have used can replace the microscopic pattern proper, provided they are of good quality. They are unquestionably better than the microscopic pattern for the study of certain details and especially for purposes of comparison.

Whenever possible, explanatory details presented for the illustrations have been based on norms which are generally recognized or at least accepted by the majority of the authors on the subject. Numerous references attest to this fact. With regard to interpretations that are still in question or are being disputed, we have attempted to present (to the best of our knowledge) all opinions, including those contrary to our own. In this way the text is expected to provide as encompassing and current a view of the field as possible.

Intensive preoccupation with a subject such as this inevitably leads to a formal conceptualization of the genesis of cervical carcinoma. This idea threads its way through the chapters of this book until it culminates in Chapter 11 in a summarizing presentation. It should be especially noted that this concept and the supporting documentation are based on the examination of approximately 100,000 large-surface serial step-sections (see Figs. 277 to 280, 282, 283, 285 to 287, and 289). Only such sections can show changes in their natural setting, permitting one to gain insights into the pathology as well as the physiology of the cervix. These insights are just not available through the intermedium of slides made from small biopsies or from unsuitably divided biopsy material. In particular, knowledge regarding localization, extent, and forms of growth of pathological cervical epithelium cannot be acquired in any other way. It will be seen throughout the book that this very knowledge, in turn, influences consideration of many related problems.

The quotation by Ribbert which opens the book is intended to point out the significance of this knowledge. Now that investigational emphasis in cancer has shifted to fields that are more esoteric and spectacular than light microscopy, perhaps this statement is no longer appropriate. Yet, we should emphasize that there are certain basic, though quite simple, rules which can be readily grasped by simple methods under suitable circumstances. These rules might then serve as the basis for more complicated and specialized deliberations. It is possible that many fine theories will be shown to be untenable merely because their foundations are weak in terms of proved facts.

Chapter Two

Terminology

Preliminary Remarks

Every nomenclatural system ought to use universally accepted terms. However, this requirement is not so easy to satisfy when dealing with changes in cervical epithelium. Until recently, confusion prevailed in the nomenclature of pathological cervical epithelium. The vast number of personal designations, principles of classification, and methods of observations has probably contributed more to complicating matters than to clarifying them.

Thus, the terminology relating to atypical squamous epithelium of the cervix alone, for example, poses a difficult problem for the reader who is not technically well informed. That such terms as *carcinoma in situ, superficial carcinoma, preinvasive carcinoma, intraepithelial carcinoma,* and *carcinoma colli stage 0* were used synonymously is at least indicated by the occurrence of the word "carcinoma" in each of them. But only the expert might be sufficiently knowledgeable to realize that *noninvasive atypical squamous epithelium* also belongs to this group.[21, 27] Finally, whether the term *markedly atypical epithelium* was used as defined by Hinselmann [25] or whether it was simply meant to denote carcinoma in situ is a matter of conjecture even for those who have mastered the subject.

In addition, the separation of minor changes from true carcinoma in situ, and their classification in various subgroups and designation by special terms has multiplied the number of concepts considerably. Those who wished to retain a general conspectus were faced with the task of grouping together the following motley collection of terms according to their meaning:

Hyperactive epithelium
Suspicious epithelium
Simple atypical epithelium
Markedly atypical epithelium
Disquiet epithelium
Atypical epithelium
Suspicious proliferative process
Basal hyperactivity
Anaplasia
Atypical hyperplasia
Dysplasie régulière à noyaux irrégulièrs
Dysplasie irrégulière
Atypical epthelial changes
Noncarcinomatous markedly atypical epithelium

Often, these terms proved to be neither interchangeable nor even equivalent.[36, 37]
A similar state of affairs was and is encountered with respect to those changes which are not yet compatible with completely developed atypical epithelium.
This chapter reflects not only the uncertainties in terminology, but also the divergent interpretations of important details. Insofar as they are recognizable regionally, these interpretations are probably due to different approaches used to identify pathological processes and conditions. Thus the individual schooled in colposcopic techniques undoubtedly develops different concepts of pathological and physiological changes as compared with the examiner who lacks this dimension and relies ex-

clusively on microscopic patterns in attempting to reconstruct relationships.

It is difficult, therefore, to designate the various states of cervical epithelium in a totally acceptable and satisfactory manner. At the very least, however, classification has uniformly designated the most important changes in the squamous epithelium, based on contributions from international discussions.[4] Unfortunately, uniformity of terminology has not been extended to all variants; yet all must be included if a discussion of this subject is to be complete. Therefore, at present it is still necessary for every writer on the subject to utilize terms which he considers most suitable but which may not yet be in general use. It is hoped that a thorough explanation of the basic concepts and terminology employed here will reduce the effect of this unavoidable disadvantage as much as possible.

Definitions

Atypia — Atypical Epithelium

Use of the term *atypia* is confined to cellular alterations which manifest themselves in deviations form the norm in size, shape, and staining characteristics, especially in regard to the nuclei. These include polymorphism, polychromatism and hyperchromatism, nuclear enlargement, changes in chromatin structure, enlargement and multiplication of nucleoli, and increased numbers of both typical and atypical mitoses.

Varying gradations or absence of one or more of these characteristics enables one to speak of more or less pronounced atypia. Atypia is not considered to be an absolute expression of malignancy. But the stronger its features are developed, the more strongly it suggests the presence of a malignant process.

In order to provide a basis for better understanding of certain diagnostic details, it is expedient to distinguish between

cellular atypia

and

epithelial atypia.

There is no contradiction here because the signs of cellular atypia are always present in epithelial atypia. In contrast to the changes seen in the single cell, however, epithelial atypia is concerned with *altered epithelial architecture.* It can be considered to be mild in extent if, in spite of cellular atypia, both *cell borders* and *layering* are still quite distinguishable. The less well-defined these architectural characteristics become, the more marked is the degree of epithelial atypia. It reaches its maximum when structural order is altogether lost. Increasing epithelial atypia usually is associated with increasing nuclear density.

The expression

atypical epithelium

is used to signify the appearance of atypical cells in the epithelium. Thus, generally speaking, it encompasses all atypical proliferations in an already well-developed epithelium without regard to the degree of atypicality. It is used primarily when there is no need to differentiate between carcinoma in situ and dysplasia.

This concept of atypia is substantively different from that of Hinselmann.[25] His designation of *simple atypical epithelium* included epithelia with "abnormal differentiation" and with "new growth of cells corresponding to cell exfoliation." That he had limited this term to abnormally differentiating epithelium appears to have been forgotten. Misinterpretation may have resulted from the need to include dysplastic epithelial changes and from attempts to translate Hinselmann's nomenclature into the language of other classifications. In the presence of "excessive cell proliferation" Hinselmann spoke of "markedly atypical epithelium," which he defined as patterns with "proliferation of germ cells and differentiating cells" or simply with "proliferating germ cells." One can easily see that this definition encompasses all atypical proliferations in the strictest sense of the word, including dysplasias as understood today.

In the development of his nomenclature, Hinselmann's basic thought undoubtedly originated from his desire to interpret classic colposcopic findings in histological terms. Most colposcopically suspicious lesions are due to certain specific growth patterns and well-defined relationships between epithelium and stroma (see p. 166). These colposcopically tractable relationships may, however, apply to both abnormally differentiating and markedly atypical epithelium. Consequently, various histological changes may present with very similar colposcopic views. Understandably enough, this discovery led to the conclusion that these colposcopic views revealed the essential area — i. e., the "matrix area" — of carcinoma. In view of this conclusion, it is logical that Hinselmann extended the term "atypia" to histological changes which did not show atypia in terms of histological pathology. Apparently he did so because they presented the "colposcopically atypical" patterns believed to reflect the "matrix area." In the interim, it has turned out that "simple atypical epithelium" plays no recognizable role in the genesis of carcinoma.[12, 26] Despite this, the unfortunate use of the term atypia has persisted, especially in German-speaking countries, and is a source of continued misunderstanding.

Carcinoma in Situ — Dysplasia

Both of these terms are used today with increasing frequency to define carcinomatous or suspected carcinomatous changes in cervical epithelium. The designation *dysplasia* is used in lieu of the terms cited in the previous section for lesions that do not yet qualify as carcinoma in situ. It is expedient to subdivide dysplasias into

low degree
and
high degree forms.

Both carcinoma in situ and the dysplasias are characterized by the features of atypia discussed earlier. The distinguishing difference is only a quantitative one. Carcinoma in situ presents the maximum of the atypia characteristics which are also distinctive of dysplasia.

Basal Hyperplasia

The designation basal hyperplasia is often equated to that of dysplasia. The term has rightfully survived because "basal cell hyperplasia or hyperactivity" at one time formed the basis for a classification of atypical epithelium. TeLinde and Galvin[47] subdivided those changes, which are today considered to be dysplasia, into three grades of basal hyperplasia. In most dysplasias the maximum increase of cell and nuclear proliferation is indeed found in the basal epithelial layers. Other authors[8, 51] have used the term to indicate that cell multiplication or cell atypia *exclusively* occurs in the basal layer. The cell layers overlying a compact layer of proliferating or atypical cells — often sharply demarcated superiorly — show no substantial variations

from normal. This picture is so characteristic that it cannot logically be included among the dysplasias. It is, therefore, appropriate to differentiate between

basal hyperplasia

and the dysplasias.
Numerical hyperplasia of basal cell elements can affect the normal basal cell of the epithelium. It appears to be an expression of increased regenerative activity of an irritation of the epithelium, thus warranting the designation *regenerative* or *simple hyperplasia*. This variety is clearly different from that form of basal proliferation which presents one or more signs of atypia and which, under high-power magnification, is reminiscent of carcinoma in situ or of dysplasia. The significance of this latter lesion is likely to be basically different and, therefore, requires that we differentiate

atypical basal hyperplasia

from the regenerative form.

Abnormally Differentiating Epithelium

Normal squamous epithelium of the cervix has a rather characteristic construction. Its architecture is determined by site-specific differentiation of the epithelium. Deviations from the basic patterns occur not only in the context of *atypia* but also in association with *disturbances of differentiation*. Well-recognized forms of differentiation, which are, however, unusual in the cervix and vagina, can result. Absence or incomplete development of glycogen-containing upper epithelial layers characterize this type of disorder. Compensatory expansion of the prickle cell layer usually occurs as a consequence. Concurrent parakeratosis or true cornification is almost a constant finding. These epithelial changes play a major role in colposcopic diagnosis. They also become very apparent by means of Schiller's iodine staining. Histologically, they may show certain variations. These may account for the diversity of terms applied to them. Treite[49] described them with expressions such as *benign prosoplastic squamous epithelium, leukokeratosis, hyperkeratosis,* and *parakeratosis*. Limburg[32] spoke of a *benign epithelium* or of one with *epidermization*. In the American literature one finds other terms like *prickle cell hyperplasia,*[23] *epidermoid hyperplasia,*[16] and *hyperplastic epithelium.*[30] French authors designate such epithelium as *dysplasie régulière.*[5, 7]
Occasionally, close relationships between these epithelial types and squamous metaplasia are stressed.[5-7, 14, 16, 18] There is little doubt that such relationships exist. Unusual differentiation is actually often seen in metaplastic processes. One should, however, not overlook the fact that this unusual differentiation also appears in epithelial fields that are rather far removed from the mucosa and well beyond the glandular field (Fig. 15). The colposcopist must come to terms with this fact daily. Lastly, the cervical or vaginal epithelium is liable to undergo such unusual differentiation any time it is exposed to a new type of stress, as in the case of prolapse.
Hinselmann[25] distinguished the epithelium with "*abnormal differentiation*" as *simple atypical epithelium*, as contrasted to markedly atypical epithelium (see above). Askanzy[1] promptly called attention to this contradictory use of the word atypia. The term he proposed for the epithelium that differs from normal only by its differentiation was simply

abnormal epithelium,

thus strictly separating it from atypia by the use of the word "abnormal." To avoid misunderstandings, throughout this book this type of epithelium shall be termed "abnormally differentiating epithelium."

Ectopia — Glandular Ectopia
Glandular Field — Last Cervical Gland
Epidermization

The border between ectocervical squamous epithelium and the columnar epithelium of the cervical canal is very variable, with regard to both location and character. The junction is ideally located at the external os. However, it may be formed well within the canal or out on the portio vaginalis. In the latter circumstances, the resulting appearance has often been inappropriately called *erosion* or *pseudoerosion*. This condition is of some importance in pathological processes involving the cervix. Opinions concerning its genesis and the change it undergoes toward "normal" have long been influenced by the well-known theory of Meyer[34] (see p. 52). Recently, this concept has been subjected to revision based on the investigations of a group from Cologne.[20, 39, 43] They proved that outgrowth of the endocervical epithelium onto the ectocervix took place by the mechanism of a shift of the entire cervical mucosa, i. e., by *ectropionization of the cervical mucosa*, while epithelialization of a "genuine erosion" by mucus-producing epithelium was irrelevant. The ectropionization consequently involves not only the superficial columnar epithelium but also the glands and the loose inner layer of the cervical stroma. The area occupied by the endocervical mucosa remains constant so that the shift also affects the junction between the mucosa of the canal and that of the endometrial isthmus. That this process depends on age and ovarian function is evidenced by the fact that it is predominantly associated with the reproductive period. At the menopause, the mucosa is drawn up again into the canal.

The theory of a displacement involving the entire cervical mucosa explains why the columnar epithelium which has shifted onto the ectocervix *never* consists of only a superficial layer, as might occasionally be expected if R. Meyer's theory were correct. Rather it duplicates the cervical mucosa, complete with glands and ducts. Such a perfect duplication can hardly be brought about by secondary gland formation.

Ectropionization, which is better designated by the more common term

ectopia,

is thus caused by the *displacement of the cervical mucosa*. Restitutio ad integrum or healing is therefore only possible if the displaced mucosa is drawn back into the canal again in its entirety, as can be observed after menopause.[43] If, however, the replacement by squamous epithelium is confined to the columnar epithelium of the surface or of individual glands, we are not dealing with a *displacement* of the mucosa but rather with a *substitution of its covering*. This does, by no means, rule out an ectopic location of cervical glands; on the contrary, it compels us to register

glandular ectopia,

quite irrespective of the quality of the surface epithelium.

With this in mind, it becomes clear that the site where squamous epithelium meets the columnar epithelium, the notorious *squamocolumnar junction* of Anglo-American literature, has only secondary importance as a reference point. Its location depends on both the position of the cervical mucosa and the nature of its surface. This means that the epithelial junction need not necessarily coincide with the *distal border of the glandular mucosa*, but may come to lie anywhere within the mucosal region or over an area of glandular ectopia. Considering the various possible locations in relation to the external os, we arrive at a whole range of variations, whose systematic classification largely goes back to the aforementioned group of investigators.[39, 43]

Reference points are needed, nevertheless, to reconstruct the topography of the cervix (see Chapter 4, p. 31). One might designate the external os as such a point. But every histologist knows that the cervix is frequently de-

formed on fixation, so that the location of the os in a histological section cannot be determined with absolute accuracy. Still, one can judge from its approximate position whether a given histological change is located in the canal or on the ectocervix. This does not, however, tell us anything definite about the relationship of the lesion to the cervical mucosa or, more generally, to the

glandular field

of the cervix. Yet this relationship is paramount for many problems encountered in cervical pathology. Consequently, we will consistently be faced with the question whether a given alteration has developed over a *glandular field*, i. e., in the region of glandular ectopia. In this case the point of reference which marks the border between the genuine squamous epithelium of the ectocervix and the mucosal or glandular region is the

last cervical gland

at the periphery of the cervix.[38, 43] This gland may be located near the external os, at distal or at proximal sites (Fig. 7).

Both ectopic cervical mucosa and endocervical mucosa can be covered by squamous epithelium for variable stretches. The quality of this epithelium may be variable. If it corresponds in appearance to normal ectocervical squamous epithelium or shows only unsuspicious differentiation disturbances it may be considered to have reached its final developmental stage. This condition in which the *cervical mucosa is covered by a mature squamous epithelium is usually called*

epidermization.[17, 19, 35]

Justification for the use of this rather unfortunate term probably comes from the fact that the "epidermization epithelium" at times shows a type of differentiation which is more reminiscent of the epidermis than of the structure of cervical and vaginal epithelium (see pp. 64, 192 f.). Castaño-Almendral and Beato[10] have shown by karyometric techniques that an apparently normal squamous epithelium located over the glandular field also differs significantly from genuine ectocervical squamous epithelium. Consequently, they use the term *"third mucosa"*[3] to describe an epithelium which is demarcated on one side by the last cervical gland and on its other side by the squamocolumnar junction. It thus lies between the "epidermoid mucosa" and the "glandular mucosa."

Ascending Healing Regeneration Squamous Metaplasia

The investigations of Castaño-Almendral and Beato[10] just cited confirm the known fact that squamous epithelium found in the glandular area arises as a result of new growth. If comparable at all, this epithelium best compares with the product of reparative regeneration, which not infrequently deviates from the normal structure.

This comparison is not so unlikely as it may seem, as the squamous epithelium forming in the glandular area is actually — at least in part — due to regenerative processes in the strictest sense of the word. For in some cases the mucosal area is indeed overgrown by offshoots of genuine squamous epithelium. All indications point to the fact that this phenomenon occurs where true erosions of the columnar epithelium are to be covered. Its uniqueness lies in the replacement of one form of epithelium by another.

Whether this process is also able to extend beyond the defect and undermine intact columnar epithelium, lifting and replacing it, is a question which cannot readily be answered in the affirmative (see pp. 65, 146 f.), although, according to R. Meyer's contention, "healing of erosions" in its second stage takes place in this manner. All we know is that regenerating epithelial offshoots are occasionally covered by columnar epithelium. Where this is the case, it involves extremely short stretches at the tips of the offshoots only. This observation is entirely consistent with the il-

lustrative description of "erosion healing" given by Hamperl, Kaufmann, and Ober,[19] who very appropriately called the growth of squamous epithelium advancing into the glandular area

"ascending healing."

This process usually advances from *distal to proximal*, i. e., in an ascending fashion. The peripheral squamous layer gradually decreases in height to form an epithelial wedge, which consists of few or several cell layers depending on the duration of the reparative process and finally borders on the columnar epithelium. Fluhmann[14] called this area the *transitional zone* and believed that the low epithelium corresponded to the various stages of "prosoplasia." But then, Fluhmann interprets the word prosoplasia in terms of a process more commonly known as *squamous metaplasia.*

It is undoubtedly correct that metaplastic epithelium also undergoes developmental stages that are comparable to the epithelial offshoots of ascending healing. Although Hamperl et al.[19] pointed out certain morphological details which may be useful for differentiating the two processes, differentiation will still present difficulties, whenever it is attempted on the basis of small, unclear biopsy samples, where the epithelium is removed from its natural setting and its relationship to adjacent layers is lost.

Therefore, it appears to be expedient to define undifferentiated or partially differentiated epithelium without regard for its origin. Whenever it cannot be determined with certainty whether it originates from the *regenerative process of ascending healing* or from

regenerative metaplasia,

it is thus termed

regenerative epithelium.[15]

Surely, squamous metaplasia occupies an important place among pathological lesions of the cervix. It is a process in which the columnar epithelium at the surface and in the glands is replaced by squamous epithelium through the growth of a new cell type. This replacement by way of a special process other than direct transformation of differentiated columnar cells in squamous cells is termed

indirect metaplasia

according to Fischer-Wasels.[13] It is more commonly known as

squamous metaplasia.

Synonymous terms refer to related or special aspects of the same process. Terms such as epidermization or epidermoidalization should be reserved for the description of the end stages of a condition whose origin is not always evident (see above). Fluhmann[14] used the word *prosoplasia* previously expressed by Schridde[44] to support his opinion that the replacement of columnar epithelium by a squamous layer signifies a more advanced degree of differentiation. On the other hand, Schiller[41] and Treite[49] correctly designated the acanthosis and the cornification process of the normally uncornified squamous epithelium as *prosoplasia.* The term *reserve cell hyperplasia*[2, 5, 6, 7, 16, 21, 27, 48] is interpreted to denote multiplication and accumulative piling of cells, which trigger the metaplastic process. These cells have been called variously *basal cells,*[31] *subcolumnar basal cells,*[9] *cambium cells,*[13] *indifferent basal cells,*[40] *subepithelial cells,*[40] and, perhaps most appropriate, simply

subcolumnar cells.[42]

Von Haam and Old,[18] among others, named the first increase in these cells *reserve cell hyperplasia* and spoke of an *immature* or *incomplete squamous metaplasia* at the beginning of the differentiation of metaplastic epithelium. De Brux and Dupré-Froment[5-7] distinguished reserve cell *multiplication* from *hyperplasia.* They were evidently familiar with an intermediate stage of *multiplication combined with discrete hyperplasia.* In conditions of disturbed metaplastic architecture, von Haam and Old[18] found *reserve cell disorder* or atypical *reserve cell hyperplasia*