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Continuation of Ergebnisse der Pathologie

70

Cervical Cancer

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With 115 Figures

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Preface

Few subjects in gynecology, let alone in medicine in general, have provoked such interest or study as cervical cancer. Although the wealth of monographs and books published on the subject would seem to obviate the need for more, the great advances made in the medical sciences and in gynecological experience and techniques in recent years call for, if not require, a new book on cervical cancer to bring together the latest ideas and trends in its methods of study, diagnosis, and treatment.

Although precancerous lesions have become more common, the number of women developing invasive cervical carcinomas has not increased, owing in part to programs of patient education, in part to screening examinations sponsored by the government. The gynecologist is now able to detect with well-tried and proved techniques precancerous states of the cervix, and to treat these effectively before they become invasive cancer.

Accordingly, recent interests in cervical cancer have shifted from the classic description of invasive carcinoma to newer studies of cause, diagnosis, therapy, and terminology of its precursors. As the reader will learn, epidemiological studies as guides for the future account for, and justifiably so, an important part of this book. New knowledge about changes in the morphology of cervical carcinoma confirms its dependency on hormonal stimulation. Furthermore, modern experiences serve to explain which therapy is best.

Overlapping of concepts and opinions between some chapters could not be avoided. On the contrary, it was sanctioned, for it is an edifying experience in itself to realize how alike these opinions are, although the individual authors expressing them view their subjects from quite different standpoints.

The purpose of this book was not to imitate a handbook, to cover the whole field as a broad review, but rather to concentrate in detail on subjects of current and special interest and to register latest developments.

To all authors I extend my special thanks for cooperating so amiably and well in preparing their reviews. Their high standards have guaranteed the success of this endeavor. I express my gratitude to Springer-Verlag for its usual but nonetheless appreciated care in publishing this book and in preparing illustrations of such perfection.

Mannheim/Heidelberg GISELA DALLENBACH-HELLWEG

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P. STOLL and P. STOLL jr.

A. Introduction

Gynaecological oncology comes close to meeting in theory and practice the ideal requirements of general oncology, i.e. suitable model concepts of epidemiology and aetiology are available. The pathogenesis, morphological development and clinical course of cervical cancer are well-known, and it is thus possible to make a prognosis with a high degree of certainty.

For many years gynaecologists have been concerned with a wide range of problems. Many important results have been achieved in research; new methods of investigation have been developed and rapidly put into practice on a large scale. Gynaecological morphology represents a special field within general pathology; gynaecological histology and gynaecological cytology are often carried out by specialists in gynaecological departments, but the family doctor conducts the examination of the patient and takes the material for morphological investigation (screening) in his office. The present organisation of gynaecological oncology is shown in Fig. 1.

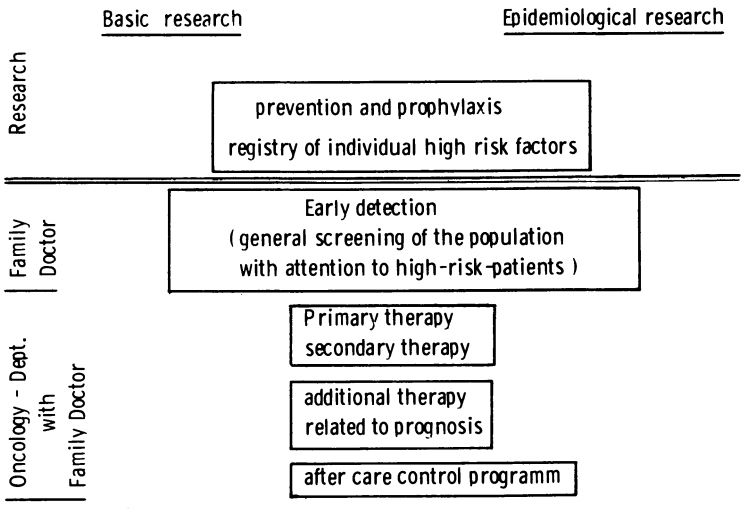

Fig. 1. The present organisation of gynaecological oncology

Close cooperation between the general practitioner, specialists, the cancer hospital and social institutions involved in aftercare will provide the best results. On the other hand, women must be encouraged to undergo cancer detection check-ups. In 1974, 5 552 773 women (31%) in the Federal Republic of Germany underwent gynaecological examination including cytology in the Cancer Prevention and Early Detection Programme of that year (financed by the social security system). According to social status (as assessed by membership of profession-specific insurance agencies), participation varied between 20% and 64%.

As regards further development, the following steps are necessary:

1. The factors leading to the formation of cancerous lesions must be investigated and eliminated *(primary prevention)*,

2. The preinvasive stages of carcinoma must be eliminated *(secondary prevention)*,

3. The early stages of carcinoma must be detected and eliminated *(early limited therapy)*,

4. Existing cancerous lesions must be removed in their entirety or destroyed *(individualised therapy* to suit the stage of disease),

5. Advantage must be taken of all possibilitites of *supplementary therapy*,

6. Particular attention must be paid to *rehabilitation and aftercare*, from the somatic, psychological and social points of view, of the patient who has been treated for cancer,

7. All cases of cancer must be recorded according to specific criteria to facilitate *statistical evaluation.*

Several of these general demands are met in the case of cancer of the collum:

1. Risk groups can be established.

2. Preventative screening can be carried out at low cost; it is painless and sufficiently safe.

3. The extent of the tumour can be described using the "FIGO" or the "TNM" system. Treatment can be standardised and can be operative or radiological or a combination of both methods. In addition, cytostatics and hormones can be used therapeutically.

4. Immunological questions are at present under study and may one day lead to an improvement in rates of healing.

5. Aftercare following primary treatment can be organised on the basis of cooperation between the hospital where treatment was carried out and the family doctor (gynaecologist and/or general practitioner).

Since it is possible to make a prognosis for the various stages of the disease on the basis of the available world-wide statistics, the most suitable type of aftercare treatment can be chosen accordingly.

Decisive for the prognosis of a patient with cancer of the collum ist the *timing of the diagnosis* and the *initiation of adequate primary therapy.* The chances of cure decrease rapidly with increasing extension of the tumour. Intra-epithelial neoplasia preceding an invasive growth can be cured by local excision only in almost 100% of cases. Doctors must concentrate their efforts on the early diagnosis of precancerous lesions and early invasive cancer.

B. The Organisation of Early Diagnosis of Cervical Lesions

The general practitioner is responsible for taking down the family and personal history (including the history of bleeding). In the examination he should palpate the abdomen, inspect the vulva and vagina, cervix (using a speculum), take a smear, conduct internal palpation and examine the rectum and breasts. The general practitioner has a certain advantage over the specialist and the hospital by virtue of his more personal contact with the patient. In addition to the above procedures, the specialist is responsible for colposcopy, colpomicroscopy, examination under anaesthesia, taking of an abrasion specimen, probing, streak abrasion, ultrasonic examination and X-ray. The hospital has the further responsibilities of computer tomography, hormonal investigation, laparopelviscopy, operation and postoperative consultation as well as the aforementioned procedures.

Each gynaecological examination serves at the same time as a search for cervical carcinoma or its precursors. In countries in which large-scale screening programmes have been introduced, the screening procedure corresponds to that of a regular gynaecological examination. It is necessary for all steps of the examining procedure (see Table 1) to be carried out with care, since indicative symptoms of the disease are not to be expected in the case of the preclinical and early stages. Whereas in curative medicine the patient's complaints and worries offer an indication for further diagnostic steps and specific investigations can be instituted objectively, this is not the case in preventive medicine. The investigative procedure must cover all steps which could lead to the early discovery of an existent neoplasia. The investigative procedure is therefore programmed as outlined below:

Table 1. Programmed gynaecological examination in practice

1	Family history, personal history, history of bleeding				
2	Recumbent on examination chair, palpation of abdomen, inspection of vulva, adjustment of portio with speculum, inspection				
3	*Indirect smear for vital cytology*		*Evaluation: immediate*		
	Platinum loop	Vaginal secretion	Vaginal flora	Function	Normal
	Fornix vaginae	Phase contrast (vital prep.)	Leucocytes		Suspicious
			Degree of purity		
4	*Colposcopy*				
	Surface of portio 				Normal Suspicious Positive
	(Ectopia, transformation, leukoplakia, mosaic, micro-Ca, macro-Ca)				
5	*Direct smear*				
	Cotton-wool swab	From surface of portio or from site of colposcopic lesion and from cervical canal	*Evaluation in laboratory*		
	Ayres spatula		Leucocytes	Function	Normal (PAP. I and II) Suspicious (PAP. III repeat) Positive (PAP IV and V)
		Papanicolaou stain			
6	Gynaecological examination (bimanual palpation)				
7	Rectal examination				
8	Mammary inspection and palpation Instructions for regular self-examination				
9	Discussion with patient				

C. Individual Investigative Steps in Gynaecological Practice

I. Case History

The case history gives an indication as to whether the patient is at risk.

Risk factors for cervical carcinoma are listed by *Rotkin* (see, in particular, Chap. 4, Table 5), and on the basis of these factors the medical practitioner classifies his patients into three groups: low risk, medium risk and high risk. The *lower-risk group* comprises those (a) with no period of sexual activity, (b) using 'barrier' contraceptives, (c) who have undergone hysterectomy, (d) beyond 60 years of age and (e) who have cervical cytological examinations at regular intervals throughout their life. The *medium-risk group* comprises those (a) having sexual activity, (b) having had multiple abortions and/or deliveries and (c) with persistent cervical ectropion. Early onset of sexual activity, multiple sexual partners, multiple marriages and low social class are the criteria which characterise the *high-risk group.*

On the basis of the above classification, the following screening procedures are recommended:

Low-risk group: Controls at long intervals or no regular controls.

Medium-risk group: Cervical Pap smear every 2 years; after two negative smears, smears at 3-year intervals.

High-risk group: Annual Pap smear.

When taking the patient's history the gynaecologist should ascertain the "biological age of the cervix" according to the equation:

biological age of cervix = age of patient + sexually active years before 20th year

Increasing age increases the risk: The average age of patients with invasive cervical carcinoma is 47 years (micro-invasive carcinoma, 43 years), for carcinoma in situ, 37 years and for dysplasia, 27 years. Subjective observations of the patient are not necessarily indicative of the presence of an intra-epithelial neoplasia. Accounts of reddish-brown fluor, bleeding anomalies, contact bleeding and uncharacteristic pain should, however, lead to increased intensity of investigation.

II. Examination of the Ectocervix by Inspection

The os externum can be seen with the naked eye: In women who have not yet given birth it is pitted, while in those who have given birth it is transversely split. The examining gynaecologist can distinguish a red spot on the ectocervix, a so-called erythroplasia, with the naked eye, without being able to differentiate it further. Such a change is common in women who have given birth and also in those taking hormonal contraceptives. It is necessary to carry out a colposcopic examination and take a cytological smear to clarify the change.

In the case of *contact bleeding* of the ectocervix when it is touched with a cotton-wool swab or spatula, there is always a suspicion of a neoplastic or preneoplastic lesion.

Pronounced invasive carcinoma is often visible to the naked aeye and is characterised by ulcerous lesion (ulcer formation) or exophytic growth.

In younger patients the neoplastic process is more likely to be localised on the surface of the ectocervix. In older women, however, and particularly in postmenopausal women, the location of the neoplasia retreats into the cervical canal. Under these circumstances visual observation of *bleeding from the cervical canal in older patients* is very suspicious and calls for a removal of tissue (curettage and conization).

III. Colposcopic Examination

Colposcopy provides a method of stereoscopic surface observation, whereby the diagnosis is improved by technical means such as green filter, and by tests involving chemicals, such as acetic acid and iodine.

The following factors affect the picture:

1. Colposcope (binocular)
   a) Light intensity of the source of illumination
   b) Enlargement factor (6–40 ×)
   c) Colour filter (green)
2. Blood supply to organ
   a) Arterial
   b) Venous
3. Course of vessels and their filling state
   a) Normal
   b) Atypical
4. State of surface
   a) Dry–moist (light reflexes)
   b) Level
   c) Type and density of tissue
   d) Cell structure
5. Reaction to reagents
   a) Acetic acid solution (for mucus count)
   b) Vasopressive drugs
   c) Staining solution (Lugol, toluidine blue).

The nomenclature was originally drawn up by the discoverer of the method, *Hans Hinselmann,* but has been amended several times over the years, especially since the introduction of cytology, directed biopsy and comparative histological examination.

The findings yielded by colposcopy are now divided into four main groups:

1. Normal findings:
   a) Original squamous epithelium
   b) Ectopia (original columnar epithelium)
   c) Transformation zone
2. Abnormal findings: see Table 2.
3. Differential findings:
   a) Inflammation

Table 2. Abnormal findings of colposcopy (World Congress on Pathology of the Cervix and Colposcopy, 1978, Orlando, United States)

	Not suspicious	Suspicious
	Biopsy unnecessary	Biopsy necessary
Mosaic	Regular Fine – on a level Acetic acid reaction +	Irregular Difference in level Acetic acid reaction ++
Punctation	Regular Fine – on a level Acetic acid reaction +	Irregular Difference in level Acetic acid reaction ++
Leucoplakia	Fine, slightly elevated	Lumpy, papillary, difference in level
Acetic acid – white epithelium	Fine – on a level Acetic acid reaction +	Difference in level Acetic acid reaction ++
Atypical vessels	Absent (–)	Present (+)

b) Erosion
c) Decidua
d) Polypi
e) Condyloma
f) Papilloma, etc.

4. Indecisive findings:
   a) Squamocolumnar junction not visible
   b) Colposcopy not possible
   c) Uncertain colposcopic findings

Colposcopy may be repeated as often as necessary, since it causes neither changes in the epithelium nor trauma. The quantitative components of the diagnosis are its particular task, i.e. ascertainment of the location and extent of surface processes. On the other hand, it is also suitable as a check on the progress of the lesion and is the basis for the directed biopsy carried out at the colposcopically suspicious site.

IV. Cytology

1. Vital Cytology

It is possible for the gynaecologist who has been trained in and is interested in cytology to carry out a cytological examination of the vaginal secretion during the consultation (vital cytology). For this purpose it is best to use a phase-contrast microscope or an interference-contrast microscope.

The immediate evaluation of secretion taken from the upper side-wall of the vagina with a platinum loop provides the following information:

1. *Functional phase* (hormonal stimulation of the vaginal epithelium);

2. *Biology of the vagina,* vaginal flora (Döderlein, cocci, mixed flora, *Haemophilus vaginalis, Monilia, Trichomonas*);

3. *Inflammation* (presence of leucocytes in the secretion, cytolytic and autolytic changes in the squamous epithelium, well-maintained or degenerate leucocytes, lymphocytes and plasma cells);

4. *Bleeding* (presence of erythrocytes in a more or less good condition);

5. Suspicion of the presence of abnormal cells.

If the vital preparation consists mainly of autolytic cells or if there is a relatively severe inflammation, it is not a favourable time for taking a Papanicolaou smear for subsequent cytological laboratory diagnosis because of the inflammatory changes present. The vaginal area must first be cleared of bacteria by means of preliminary treatment and the proliferation of the vaginal epithelium must be reinforced. Various medical products are used for this purpose. They are applied locally in the vagina; on the one hand they have an antibiotic effect and on the other hand they bring about a proliferation of the vaginal epithelium (oestrogens). By taking this measure the number of unusable cytological laboratory smears can be greatly reduced.

2. The PAP Smear (Papanicolaou Test)

A direct smear from the point at which the lesion is to be expected (ectocervix and endocervix) is the qualitative component of the search for neoplasia. It is possible to say with a high degree of certainty that an epithelial lesion is present, without being able to state with certainty exactly where it is. The correct method of taking the smear, the immediate fixation of the preparation, the subsequent staining and reporting by a well-trained cytologist are decisive for the accuracy of the result.

a) Technical Procedure

1. Instrumentarium: cotton-wool swab, wooden spatula, plastic spatula, glass-slide; fixative;

2. Accompanying form (*must* be correctly filled out);

3. Careful removal of excessive quantities of mucus or secretion;

4. In the case of massive inflammatory changes diagnosed by vital cytology, treatment of the inflammation to avoid unnecessary, unusable Pap smears;

5. Removal of cell material separately from the surface of the portio and the cervical canal;

6. Transfer of the cell material to the glass slide by rolling off the cotton-wool swab or by scraping off the spatula;

7. Immediate fixation;

8. Delivery to cytological laboratory.

The nomenclature which was originally suggested by Papanicolaou has since undergone many modifications and varies geographically, but basically it consists of three groups: normal, suspicious and positive.

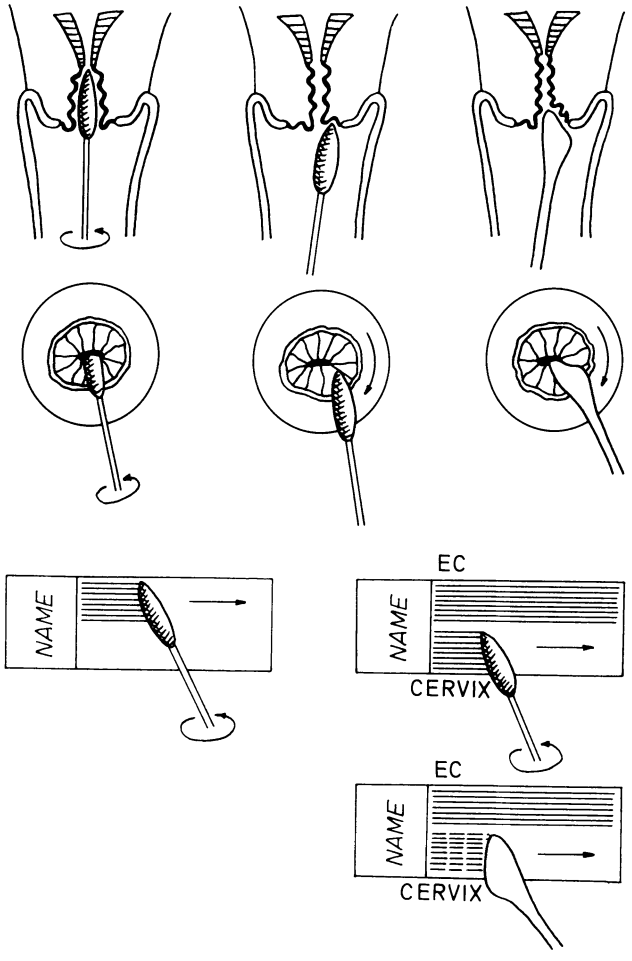

Fig. 2. The preparation of a PAP smear. *EC*, endocervical canal. (*Brunner*, private publication)

The above method of taking a cytological smear (see also Fig. 2) in the doctor's practice is a screening method which whould extract a small number of suspicious cases for further investigation from a large number of unsuspicious cases. The three distinctions mentioned, normal, suspicious and positive, are sufficient for this routine cytology. A positive result demands immediate histological clarification. A suspicious

result should in the first place be followed up by further cytological check-ups. If these are also abnormal then the diagnosis must be further clarified by removal of tissue. See also Table 3 regarding the classification of cytological findings.

Table 3. Classification of cytological findings according to the Mannheimer Cytologieschule, University of Heidelberg (*Stoll* 1975)

Group	Cytological finding	Further measures to be taken
I	Normal	Repeat examination in one year
II	Inflammatory, regenerative, metaplastic or degenerative changes. Cells of hyper- and parakeratoses	
III	Intense inflammatory or degenerative changes and/or insufficient material for study	Pap smear to be repeated soon, eventually with estrogen clearing
III D	Cells that probably come from a mild to moderate dysplasia	Cytological control in 3 months
IV	Cells that probably come from a severe dysplasia or a ca in situ	Histological clarification (conization)
IV E	Endometrical glands and stromal cells after the menopause	Histological clarification by curetting endocervix and endometrium separately
V	Cells that most probably originate from a carcinoma or another malignant lesion	Histological clarification by conization or biopsy
0	Inadequate for diagnosis (too little material, fixation artefacte, and etc.)	Prompt repeat Pap smear requested

3. Differential Cytology

The method known as "differential cytology" is an improved method of cytological diagnosis. It attempts to differentiate from one smear or repeated smears between:

Mild dysplasia
Moderate dysplasia
Severe dysplasia
Carcinoma in situ
Micro-invasion
Invasion

Some centres decide on the application of therapy on the basis of differential cytology. Others, including our own, use biopsy as a means of coming to a decision regarding the character and extent of the cancerous lesion (histological diagnostic safeguard) and only thereafter decide on the method of therapy.

V. Palpation

In the case of intra-epithelial neoplasia, but also in the early invasive stages of carcinoma of the cervix, palpation is uncharacteristic. If the tumour has already spread within the cervix then the following palpatory findings serve as an indication of the presence of carcinoma:

1. The coarse, rubbery nature of the portio and its lack of mobility with infiltration into the parametrium;
2. Vault-like distension of the cervix on vaginal palpation even if the inspection of the surface of the portio did not give rise to suspicion.

If the neoplastic process has spread to the superficial vaginal wall, this can be clearly felt on palpation. The extent of invasion of cervical carcinoma into the parametrium can be judged by rectal examination. During the clinical examination on admission the individual stages of the tumour are classified according to their extension locally and into the parametrium. For this purpose the FIGO and TNM systems are used.

VI. Clarification of Suspicious Screening Findings in the Specialised Hospital

In the hospital the whole diagnostic procedure as carried out in the doctor's practice, including taking of case history and gynaecological examination, is repeated. The specialised methods of colposcopy and cytology are now applied again in a more differentiated form. This is designated as differential colposcopy and differential cytology. The aim of this detailed investigation is to decide in what way and to what extent removal of tissue is necessary to confirm findings (punch biopsy, multiple punch biopsy, ring biopsy, conization).

D. Therapy

The aim of carinoma therapy is the removal or destruction of the complete neoplastic process together with its regional metastases. The fate of the patient is dependent on the execution of primary therapy suited to the extent of the lesion. The therapy is adapted to the extent and individuality of the tumour and to the individuality of the patient. Individualisation of tumour therapy means: "as little as possible, as much as necessary".

The following primary therapeutic measures are available to use:

1. Operative removal of the neoplasia and its regional metastases;
2. Radiological destruction of the neoplasia and its regional metastases.

In the case of a well-defined and limited neoplasia, the local destruction of the process by cauterization or cryosurgery can be applied as an alternative means of therapy. CO_2 laser technique is still in its very early stages.

The choice of the primary therapy is dependent on:

1. The particular location of the neoplasia from the operative point of view (easily accessible or hard to reach);

2. The histological character of the neoplastic tumour (grading);

3. The general operable condition of the tumour carrier (obesity, hypertension, severe primary disease).

The choice between limited an radical operative procedure in the case of microcarcinoma is made on the basis of the histological gradings. In the case of plump infiltration we have never yet come across an invasion of the regional lymph nodes and therefore limit ourselves to the removal of the process in sufficient healthy tissue, i.e. conization or simple hysterectomy.

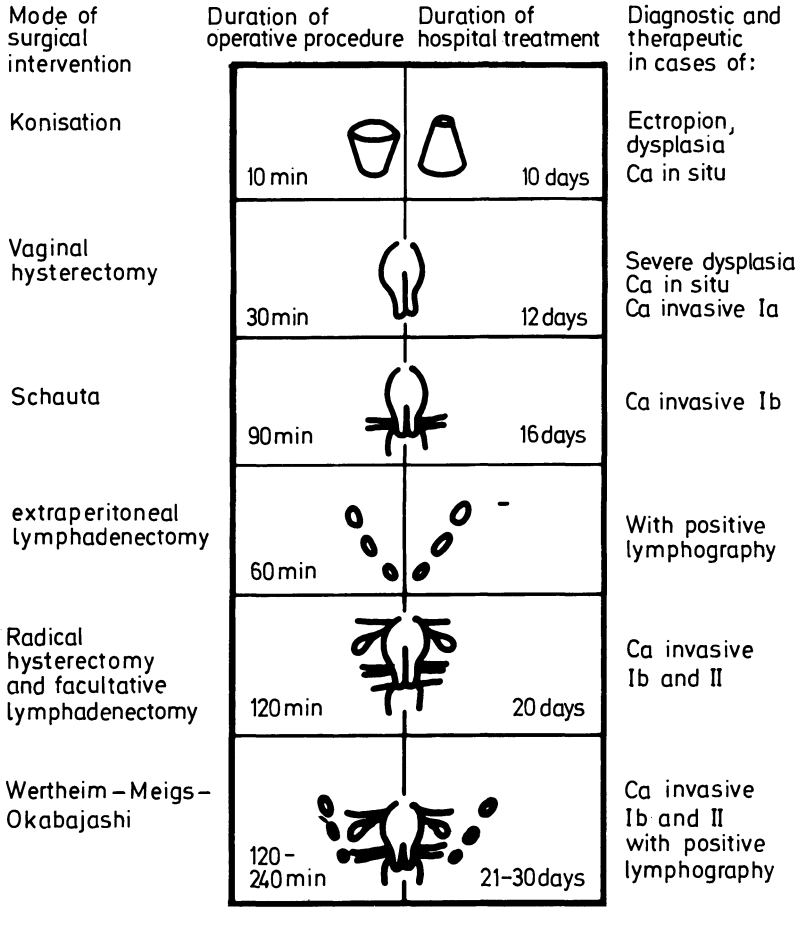

Fig. 3. Individualisation of treatment

On the other hand in the case of net-like or radicular infiltration we have seen metastases of the lymph nodes in 4% of cases. In such instances we undertake the radical operation, even in the cases of microcarcinoma (with invasion of the lymph and blood vessels). We thus take the histological individuality of the tumour into consideration in our therapy, even in the case of early carcinoma (Fig. 3).

I. Review of Preventive and Definitive Therapeutic Measures (see also Table 4)

Ectropion, ectopia, glandular erosion: The old notion of the importance of ectopia as a forerunner of a precancerous lesion repeatedly finds support. According to *Timonen* (1979) the risk of cancer of the cervix falls to 0.2 if cauterization of the surface of the portio for the restoration of an ectopia has been carried out. This is a therapeutic measure carried out in the doctor's practice, whereby after previously ensuring that the lesion is benign (colposcopy, cytology, directed punch biopsy) it is destroyed by coagulation of colliquation to enable renewed epithelisation to take place. For this purpose the following are used: Albothyl, Négatol or silver nitrate solution; thermocauterization; electrocoagulation; and cryocolliquation.

In the case of an *intra-epithelial neoplasia* in the sense of a *mild or moderate dysplasia,* the same measures can be taken. If, however, the patient is an older woman who does not wish to have any more children and in whose case there is an additional gynaecological diagnosis (chronic fluor, myoma or fibromyoma of the uterus, descensus uteri with relative incontinence), the vaginal hysterectomy with or without colporrhaphy will be considered.

In the case of *severe dysplasia and carcinoma in situ* the surgical removal of the lesion in healthy tissue is the method of choice (ring biopsy, conization, hysterectomy). In the case of limited measures an exact histological diagnosis is of great importance; this must also be the means of judging whether the lesion has been completely removed. Moreover these patients need regular follow-up examinations in order to make possible sufficiently quick recognition of a recurrence at the site of the operation.

Today cryosurgery is being recommended more and more, even for such cases, if the lesion is located at the surface of the cervix. We consider this to be responsible only if an exact pre-diagnosis is available for all areas of the lesion; even then we would recommend this method of treatment only for young women who wish to have children. In older women we consider vaginal hysterectomy the method of choice.

Naturally this problem must be discussed in detail with the patient. It must be explained that there is no reduction in sexuality, that absolute sterility is achieved but that further damaging side-effects in the somatic field are not to be expected. Thorough psychological preparation for the procedure of extirpation of the uterus is essential. Data on our own treatment during the last 10 years are shown in Fig. 4.

Table 4. Summary of individualised therapeutic measures

Therapy	Ectopia	Mild dysplasia	Moderate dysplasia	Severe dysplasia	Ca in situ	T I_a micro	T I_b T II	T III	T IV
Local									
Coagulation	x	x	(x)						
Albothyl/$AgNO_3$	x	x	(x)						
Cauterization	x	x	(x)						
Local									
Total excision (ring biopsy, conization)			x	x	(x)				
Total destruction by electrosurgery			x	x	x	(x)			
Cryosurgery			x	x	(x)				
Radium (small dose)			(x)	(x)	(x)	x			
Extended local									
Uterus extirpation Vaginal Abdominal			(x)	(x)	x	x			
Radical									
Wertheim/Meigs/ Okabajaski						(x)	x		
Radiotherapy						(x)	x	x	x

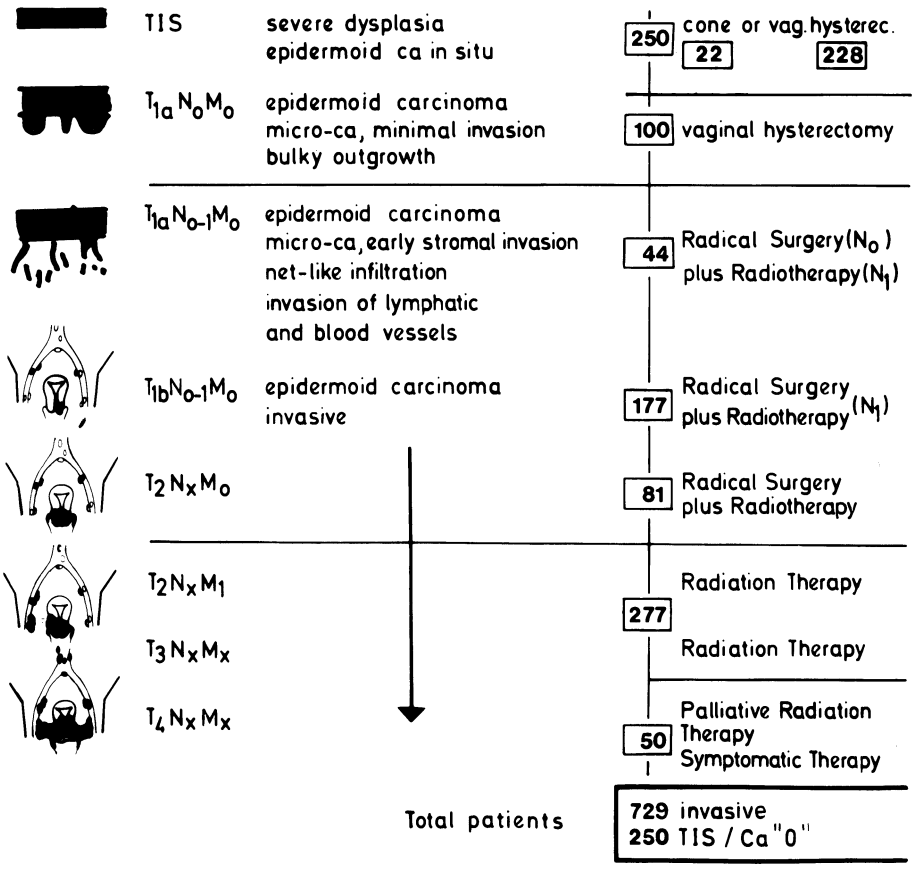

Fig. 4. Data concerning the treatment of cancer in Mannheim during the last 10 years

E. Aftercare

The success of the primary therapy depends also on the care with which follow-up examinations are carried out. The aim of these post-therapeutic examinations is to recognise secondary disease and side-effects as well as recurrences. The most common somatic secondary complications are:

- Radiation cystitis
- Radiation proctitis
- Incontinence
- Formation of fistulae
- Ureter stenosis
- Hydronephrosis
- Lymph oedema
- Adhesions
- Scar tension
- Limitation of movement
- General effects of radiation

One finds the following psychological secondary complaints:
Carcinomatophobia
Neuroses
Reactive depressions
Psychasthenia

The focal point of the aftercare is the regular general examination. The local findings in the area of primary involvement are judged following inspection and palpation. Suspicious findings are further clarified by cytology, fine needle puncture, test excision and punch biopsies. The intervals between examinations should be 3 months during the first 2 years, 6 months in the following 2 years and 12 months from the 4th year on. If suspicion of recurrence is aroused by the check-up examination, then further diagnostic steps are necessary, involving X-ray examination (lungs, skeleton, intravenous urogram, contrast investigations of intestines), cytoscopy and rectoscopy, scintigraphy, lymphography, computer tomography and laparoscopy.

By means of this wide range of investigations it is our endeavour to commence relapse therapy as soon as possible or, on the other hand, to treat side-effects or complaints arising from the primary therapy early enough to ensure the success of the primary therapy.

F. Rehabilitation

Malignant disease is not only a serious illness; it also affects the whole personality and surroundings (family and job). The task of rehabilitation is to alleviate as far as possible the suffering caused by the illness. Firstly, one must re-establish the patient in marriage and family. The preparatory work is performed by the doctor responsible for the patient in the clinic, but the real task lies in the hands of the general practitioner, who further cares for the patient and best knows her domestic situation. He is the one to be approached with particular medical, sexual and human questions.

Valuable help in this respect is provided by self-help organisations for tumour patients. These organisations have been developed on the initiative of tumour patients themselves with the intention of advising and tending to the special problems on a mutual basis.

Last but not least, the psychological care of the tumour patient plays an important role in his rehabilitation. The main point is to strengthen the patient's will to recover. After the patient's discharge from the hospital, a recommendation for pension will not be suggested right away, but the patient should continue to receive sickness benefit. By means of convalescence with clinical postoperative treatment an attempt is made to reach a general restoration of health. The patient thus has an oppottunity to examine his personal fate at a distance and to evaluate his situation more objectively.

G. Pension Recommendation (in the Federal Republic of Germany)

Whether a patient should be pensioned off is a question which should only be considered after some time has elapsed. As far as possible an attempt to reintegrate the patient in the work process should be considered before pensioning-off. An activity closely connected to the patient's previous work should be strived for. In some cases, however, retraining will be necessary. Pensioning-off often has unfavourable financial consequences, and even if it is for a limited period only, it usually leads to loss of the patient's original job. An application for invalidisation hinders the patient's will to recover. The pension application should therefore always be a last resort.

In the case of stage 0 and stage T 1_a there should be no question of a pension application, even for a limited period, since the survival rate is almost 100%. In these cases a pension would only be disadvantageous.

Invalidisation or even a temporary pension should always be avoided for tumour patients if the patient is considered to be capable in the long run of either returning to his previous job or learning a new one. It is an error with psychological consequences to grant a pension automatically to every cancer patient (*Habs* 1964, 1967). Some authors are of the opinion that in the case of a favourable prognosis – even with a 50%–75% chance of survival – a temporary pension is preferable to a life pension, above all for psychological reasons (*Husslein* and *Stöger* 1974).

In the appraisal of pension applications for cancer patients the good of the patient should always be the decisive factor. Feelings of sympathy on the part of the assessor need not be to the advantage of the patient, but can actually have a disadvantageous effect.

H. Summary

With regard to cancer therapy the gynaecologist is dependent on many different aids if he wishes to achieve a high rate of cure:

1. On the results of epidemiological research, which are helpful to him in the formation of risk groups.

2. On population education regarding the favourable effects of cancer screening programmes and the knowledge that cancer is curable if detected early enough.

3. On the local medical practitioners who are to carry out the cancer screening under special consideration of the at-risk groups and who should observe the programmed investigative stages.

4. On the cytologists and pathologists for the morphological diagnosis and determination of the extent and character of the tumour.

5. On the individualisation of the cancer therapy on the basis of points 1–4, whereby the extent of the treatment is suited to the extent of the tumour.

6. On a faultless technique under favourable conditions of anaesthesia, whereby the operations and radiation should be carried out mainly at centres where doctors have sufficient experience in the field.

7. On the co-operation with the radiodiagnostician with regard to the extent of the tumour (lymphography, computer tomography) and co-operation with the radiotherapist in the choice of operation or radiation or a combination of both.

8. On the clinical oncologist with experience in additional cytostatic therapy.

9. On the local medical practitioners for the subsequent psychological and somatic care of the primarily treated patient, including co-operation in the detection of recurrences.

10. On the statistician for the critical analysis of epidemiological and therapeutic facts. His co-operation is necessary for the improvement of early detection and therapy.

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Cervical Cytology as a Screening Method

H. HÖFFKEN and H.-J. SOOST

A. Introduction

The first attempts to describe and define morphological criteria in exfoliated squamous epithelial cells from the female genital tract date back to 1847. In that year *Pouchet* reported changes in the vaginal cell pattern during different phases of the menstrual cycle. The first prospective studies of the vaginal cycle were carried out by *Papanicolaou,* working with guinea-pigs. In 1943, together with *Traut,* he reported detailed studies of cycle-dependent epithelial changes in the vaginal epithelium of the human female. The monograph *Diagnosis of Uterine Cancer by the Vaginal Smear* appeared in 1943. In the United States his findings were soon accepted and substantiated by gyne-

cologists and pathologists alike, whereas they were not accepted to the same extent in many other countries. Cytodiagnosis now has an established place among the methods employed for the early detection of cancer and is employed throughout the world as an efficient and highly successful large-scale screening technique. The main function of exfoliative cytology in gynecologic practice is, as ever, the early recognition of cervical carcinoma and its precursors, and of other carcinomas of the reproductive system. However, it is also successfully employed for hormonal diagnosis and, by intravital techniques, for the investigation of patients complaining of vaginal discharge.

B. Collection of Material

The value of the cytologist's report on a smear depends to a large extent on the technique used for collecting material and on the quality of the smear itself. The collection of material for the cytologist should be undertaken at an early stage in the gynecologist's routine examination and should precede any attempt at palpation or any other internal procedure. It is of great importance that no medicaments of any kind should be introduced into the vagina before the specimen has been collected. Treatment of the cervix with acetic acid or iodine as an aid to colposcopy must be deferred until the specimen has been obtained. Specula must be free from disinfectants and lubricants.

After introducing the speculum, the operator takes a cotton wool swab and rubs it firmly on the external surface of the cervix including the area of the external os. The same swab is used to collect material from the lower part of the cervical canal, provided it can be entered without undue force. This is of special importance in older women, in whom the junction between squamous and glandular epithelium has retreated into the interior of the cervical canal. This junctional zone is notorious as the place where epithelial changes are most likely to occur. The operator cannot expect to obtain a representative sample unless he swabs this area. Comparative studies have proved that the procedure outlined above gives the best cytodiagnostic results (*Soost* 1976a,b).

In some circumstances it may be advantageous to make separate smears from the ectocervix and the cervical canal. This applies especially to repeat examinations, when, perhaps because of inflammatory or degenerative changes in the cell material, it has proved impossible to give a definite opinion on the first smear.

If the gynecologist sees obvious macroscopic abnormalities (erosions, ulcers, etc.) after inserting the speculum, extra smears should be taken from these areas and appropriately labeled.

There are various types of spatula which can be used instead of the cotton wool swab for taking smears. Of these, the Ayre spatula is probably the best known. However, when scrutinizing a smear taken with a spatula the observer must expect to find a different pattern of cell material, because the spatula collects proportionately more cells from the deeper layers than the cotton wool swab. In this respect smears made with a spatula are not truly comparable with smears taken with a cotton wool swab. This point is of special importance to the observer who desires to make morphological comparisons for the purpose of scientific evaluation.

Nowadays there are certain special indications for spatula smears. A spatula should be used when the cotton wool swab fails to provide adequate or representative material. This difficulty may arise in patients with abnormalities of the squamous epithelium associated with keratinization. Macroscopically and colposcopically, such lesions frequently present the picture of leukoplakia.

In the well-tried conventional smear techniques the material is transferred to a clean microscope slide as soon as it has been collected. The aim of this procedure is to spread the cells uniformly and as thinly as possible without undue force. When using a cotton wool swab this is best done by rolling it along the slide; material collected with a spatula should be carefully smeared along the surface. The material must then be fixed immediately; on no account must it be allowed to dry. Finally, the preparation is stained by the Papanicolaou technique.

C. Fixation and Staining

Excellent fixation of cell smears can be ensured by an ether-alcohol mixture consisting of equal parts of 96% ethyl alcohol and diethyl ether. The disadvantage of this mixture is the tendency of the ether to evaporate. Furthermore, as in the case of anesthetic ether, exposure to light may produce highly toxic peroxides. Such a mixture is, of course, highly flammable. Nowadays most cytologists omit the ether and use methylated 96% ethyl alcohol or 99% isopropyl alcohol instead. These fixatives give equally good results although they are cheaper than the alcohol-ether mixture and without most of its disadvantages. To ensure good fixation and staining it is essential that the preparations should not be allowed to dry. If left unfixed, the cell material will dry within as short a time as 30–60 s after making the smear. If this is allowed to happen the smear will be unusable and cytologic evaluation will be impossible. In order to achieve optimum results it is preferable to keep the fixative in Hellendahl containers with grooves on their inner walls. These keep the slides apart and prevent contamination with cell material from another patient.

Fixation should continue for at least 20 min. Prolonged immersion of the slides in the fixative causes no harm; they can, in fact, be left for several days.

Another method of fixation – more convenient but more expensive – is to spray the slide with a polyethylene glycol spray. This is applied only to the upper surface of the slide. After drying for approximately 10 min the preparation is ready for further processing or dispatch. Here again, it is essential to prevent the smear from drying before it is fixed.

Other techniques – now seldom used – are fixation in 90% acetone or in an alcohol-glycerol mixture in the proportions 5:1.

When using ethyl alcohol it is important to avoid too low or too high a concentration. In the first case fixation will fail because of the excessive water content, while the use of absolute alcohol is likely to cause conspicuous shrinkage artifacts because too much water will be extracted from the cells.

To ensure hemolysis of erythrocytes which might otherwise obscure the picture, acetic acid may be added to the fixative in the form of glacial acetic acid 3% by volume.

The aim of all these measures is to ensure the best possible preservation of cell structures so that after staining the cells will be in good condition for morphological evaluation. Fixation in alcohol denatures the cell proteins and produces a "snapshot" of the biochemical activities of the cell, visible to the observer in the nuclear and cytoplasmic structures and their staining properties. These appearances are, of course, artifacts. Nevertheless, provided an unchanging technique of fixation and staining is adhered to, the appearances will be consistent and will provide a firm and reproducible basis for morphological assessment.

When fixation has been completed the smears are stained by the method devised empirically by *Papanicolaou* in 1942 and since modified on many occasions. It must be adapted to suit the material received for examination and the technical facilities for hand or machine processing.

The staining of fixed cells is based on the fact that the various components of the cell have differing affinities for dyes. The result is a colored image of their structure, from which conclusions regarding their biologic behavior can be drawn.

The wet-fixed preparations are taken through a series of alcohol-water mixtures of decreasing concentration ending in pure water, because the hematoxylin used for nuclear staining in the next step in the process is in aqueous solution. Hematoxylin is generally used by a process of regressive nuclear staining, i.e., the slides are first overstained and this is then corrected by partially removing the stain. This process of differentiation is carried out immersing the slides in very dilute aqueous hydrochloric acid. The acid is then rinsed off with running water. At the same time the ionic content of the tap water effects some degree of neutralization, which can be enhanced by adding lithium carbonate solution. The result is known as "blueing" of the nuclei. In one well-known modification of this step in the staining process, alcohol containing ammonium hydroxide (1.5% ammonium hydroxide in 70% alcohol) is employed and the hematoxylin stage is curtailed. In this modification, washing with tap water is omitted. This method is mainly employed in urinary and gastric cytology. When stained by this procedure, the nuclei remain dark blue or violet and the cytoplasm is decolorized. The cell material is then dehydrated by taking it through an ascending series of alcohol concentrations and is thus prepared for further treatment with alcoholic dye solutions. The next step is to stain the cytoplasm with orange G. After immersion in two baths containing 95% ethyl alcohol, the slides are further stained with EA 50, a polychrome dye. The orange G gives the cytoplasm a reddish orange hue, while EA 50 confers a blueish tone. Surplus dyes and any residual traces of water are removed by subsequent immersion in 95% alcohol, xylol-alcohol, and pure xylol. The last step is to mount the preparation with a cover glass. Various substances are available for this purpose, e.g., Caedax, Eukitt, or Canada balsam.

In addition to *Papanicolaou*'s original empirical method, numerous modifications have been employed, among them methods based on polychrome dyes of other compositions such as EA36, EA 31, or EA 65. EA 36 has a somewhat higher concentration than EA 50. EA 31 tends to emphasize the degree of cyanophilia. In EA 65 the light green solution is 0.25% instead of 0.5%. In general, the differences in the staining produced by these polychrome dyes are comparatively minor.

To avoid imperfections such as overstaining or stain precipitates which make the cytologist's task more difficult, it is essential that the staining procedures used in the laboratory be kept constant. Furthermore, they must be adjusted to the number of preparations to be stained and the frequency with which staining is carried out. These

factors will determine the choice between hand or machine staining. In order to ensure consistent staining it is most important that the dye concentrations should be kept constant. We use a machine staining technique. In the Zytochromat the containers are of 300 ml capacity, while the Shandon machine has containers of 400 ml. These machines have a daily capacity of 500 and 650 slides respectively. After each batch has been processed, the staining solutions, rinsing fluids, and dehydrating solutions are completely replaced by fresh materials. In laboratories handling fewer slides and performing the staining procedure at irregular intervals it may be necessary, for various reasons, to renew the staining solutions after processing a relatively small number of slides. A useful guide to the need for fresh stain is the decrease in the intensity of nuclear staining.

The hematoxylin must be filtered every day to remove the oxidation layer on the surface. For the other stain solutions filtration at 2-day intervals is sufficient. To avoid evaporation or absorption of water vapor from the air the storage containers must be kept tightly closed, and the staining solutions must be stored in a cool place in the dark. Xylol turns cloudy as it becomes contaminated with water and must then be replaced. When changing the solutions it is important to clean the jars carefully so as to avoid contamination with detached cell material which has accumulated at the bottom. For the same reason, it is essential not to touch the surface of the slide when applying the mounting fluid.

D. Normal Smears

I. Identifiable Cellular and Noncellular Elements

A correctly made smear should contain cells from the surface of the ectocervix and the endocervix. Under physiological conditions the vagina and ectocervix are covered by nonkeratinized squamous epithelium several layers thick. Table 1 gives an impression of the histologic structure of the squamous epithelium at this site. It shows the cells identifiable by the cytologist with their appropriate characteristics, their cytometric data, and the four-stage maturation scale by which the cells are classified. The cytologic findings are discussed in detail in the subsequent sections.

The cervical canal is lined by tall columnar epithelium, which consists of a single layer of secretory or glandular cells and ciliated cells. Well-preserved fragments of this epithelium are sometimes encountered in cytologic preparations. In profile, they present as tall columnar cells with basal nuclei and with or without cilia. Viewed from above, they have the appearance of small polygonal cells, sometimes forming clumps which show a characteristic honeycomb pattern (Figs. 1, 2).

Debris, bacteria, mucus, and various cells from the blood are also encountered in smears. Squamous cells are by far the most plentiful, but in a properly made smear some endocervical cells should always be found. The presence or absence of endocervical cells can nevertheless not be considered proof as to whether the smear has been taken from the correct site.

Table 1. Histology and cytology of normal squamous epithelium from the vagina and ectocervix

Histology	Cytology	Cytometry[a]	Proliferation grade
Basal cell layer (stratum basale)	Basal cells, basophilic with dense cytoplasm, nucleus round or oval	C 12–20 μm N 8–10 μm	Not seen in normal smears
Parabasal cell layer (stratum spinosum profundum)	Parabasal cells, basophilic with dense cytoplasm, nucleus round or oval	C 15–25 μm N 8–10 μm	1
Intermediate cell layer (stratum spinosum superficiale)	Small intermediate cells, polygonal, basophilic, pale-staining cytoplasm, nucleus vesicular, with fine granules	C 20–40 μm N 7– 9 μm	2
Superficial cell layer (stratum superficiale)	a) Large intermediate cells, polygonal, basophilic, eosinophilic, nucleus still vesicular	C 40–60 μm N 6– 8 μm	3
	b) Surface cells, polygonal, eosinophilic, basophilic, nucleus pyknotic	C 40–60 μm N 6 μm	4

[a] C, cell diameter; N, nuclear diameter.

Single cells or cell clumps from the endometrium may also be present, especially in smears from the cervical canal. Their occurrence must be regarded as abnormal except in smears taken during or shortly after menstruation. The appearance of endometrial cells at other times or in a postmenopausal woman should prompt the cytologist to have the smear repeated or to initiate further investigations to exclude pathologic changes in the endometrium.

In the presence of disease, any or all of these cells may undergo conspicuous changes in their cytologic appearances. These are discussed in detail in the following sections.

If there is a breach or defect in the epithelium, cells of mesenchymal origin – usually fibrocytes – may occasionally be encountered.

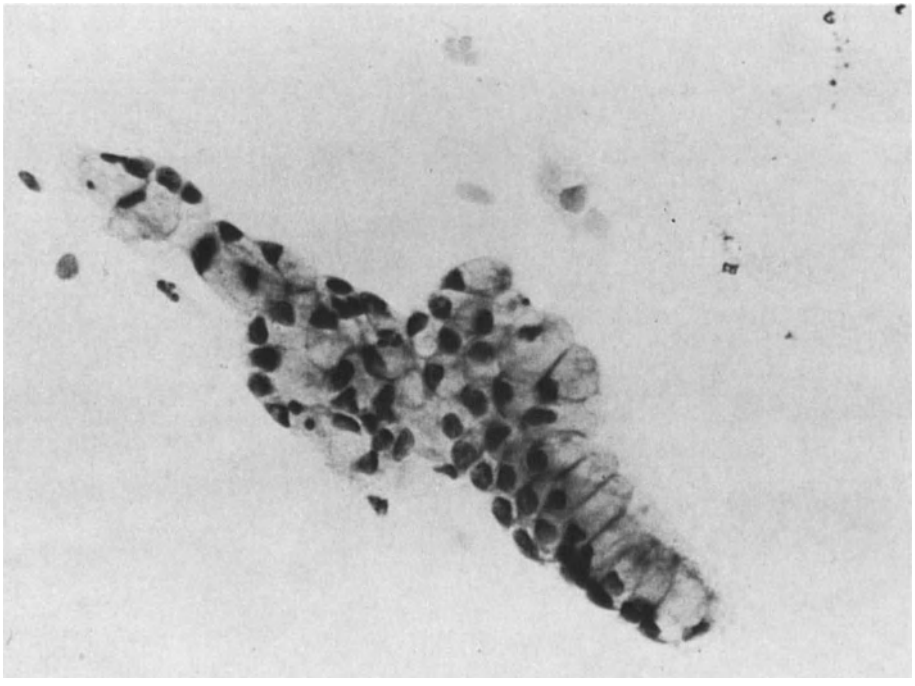

Fig. 1. Endocervical glands in side view, so-called palisade formation. × 25

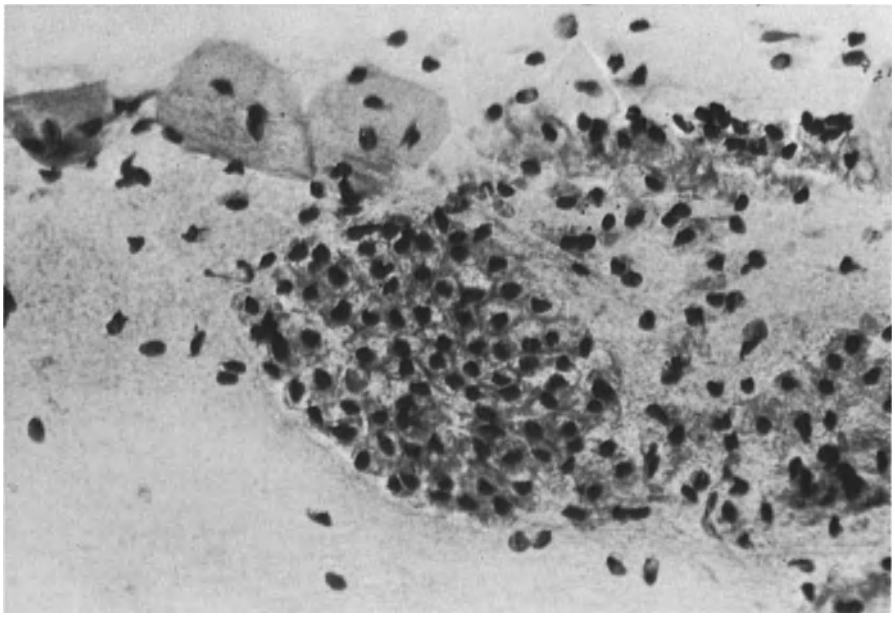

Fig. 2. A group of endocervical gland cells seen from above, so-called honeycomb pattern. × 40

II. Smears from Healthy Women

As cytology is employed as a screening method for the early detection of cancer, it is only to be expected that the vast majority of smears will show normal appearances. The incidence of suspicious or positive smears is of the order of only 1%–2%.

The pattern of the exfoliated cells depends on the stage of the menstrual cycle. Mature squamous epithelium cells generally lie singly or in loosely connected groups. They are polygonal and have a translucent cytoplasm which may be cyanophilic or eosinophilic. Large intermediate cells have a vesicular, centrally situated nucleus. Depending on the degree of cytolysis, the preservation of their cytoplasm varies from good to poor. The fully mature surface cells are distinguished by their mainly eosinophilic cytoplasm and their pyknotic nucleus (Fig. 3). During the process of cell maturation, the surface area ratio between nucleus and cytoplasm shifts from 1:3 in the basal

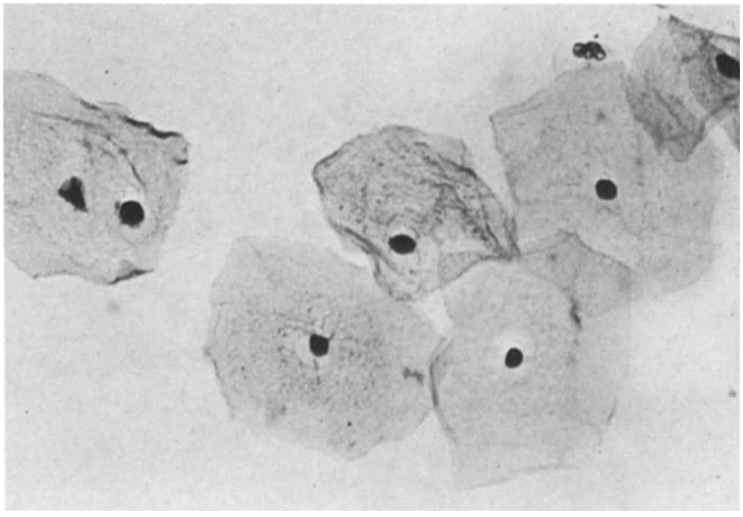

Fig. 3. Surface cells. × 40

cell to 1:100 in favor of the cytoplasm in the mature surface cell. Small dark particles, regarded as keratohyalin granules, are occasionally seen in the cytoplasm of the surface cells. The presence of occasional leukocytes in the smear should not be thought of as abnormal. In smears made with a cotton wool swab, a predominance of cells from the deeper layers suggests a deficiency of follicular hormone. Cells from the deeper layers are frequently encountered in smears prepared with a spatula and their presence does not necessarily indicate any lack of follicular hormone. The smaller intermediate cells have more or less the same appearance as the more mature cells, though on a reduced scale, but they have a more deeply basophilic cytoplasm and a somewhat larger nucleus (Figs. 4, 5).

Parabasal cells are usually rounded in outline and more or less equal in all diameters. Those derived from the deeper layers show increasingly intense cyanophilic staining of

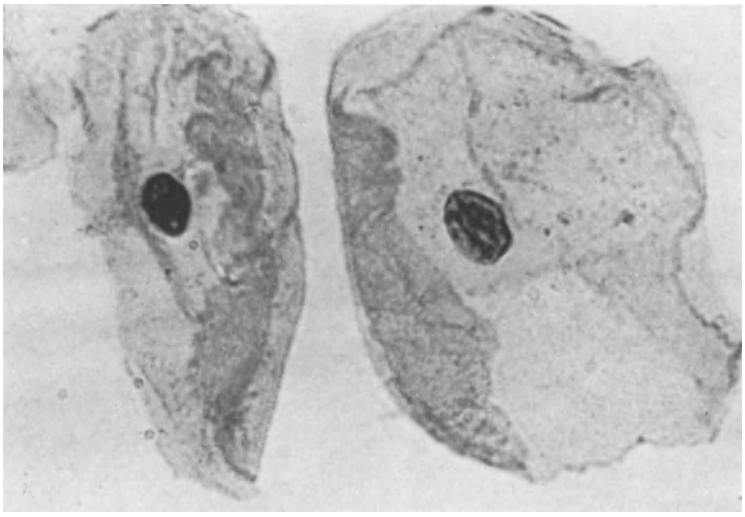

Fig. 4. Large intermediate cells. × 63

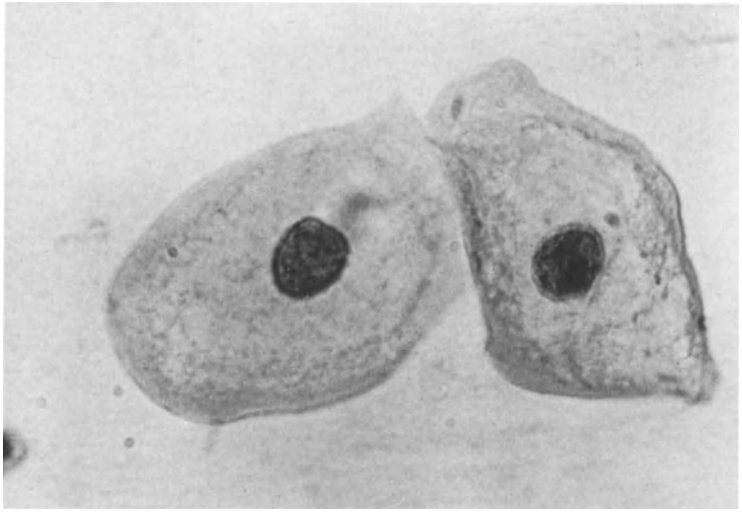

Fig. 5. Small intermediate cells. × 40

their cytoplasm. The nucleus is centrally situated, round or oval, and shows a fine chromatin structure (Fig. 6). Like the reserve cells of the cervical canal, basal cells are met with only when there is increased proliferation in the germinative zones and are not encountered when the state of the epithelium is normal.

Normal smears from women of reproductive age are generally characterized by a relatively clean background with Döderlein bacilli. In conjunction with lysozymes from the cells, Döderlein bacilli break down intraepithelial glycogen to lactic acid, which is chiefly responsible for the acid reaction of the vagina. The acid reaction of the vagina constitutes a biochemical barrier to other microorganisms, most of which

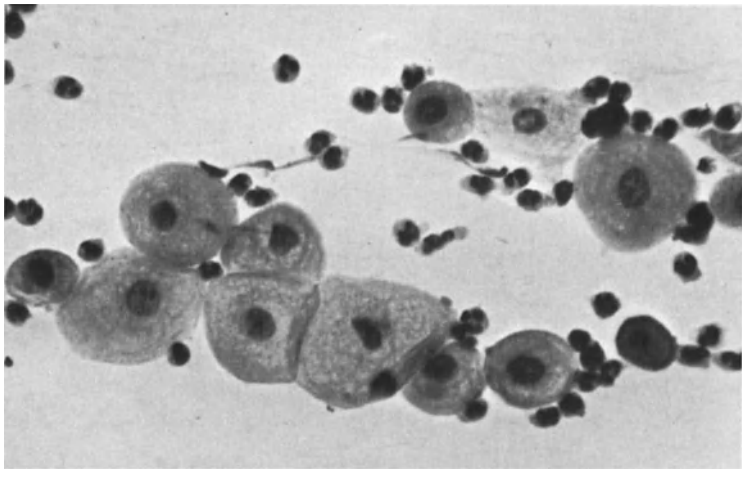

Fig. 6. Small and large parabasal cells. × 40

prefer to grow under alkaline conditions. The cytolysis of intermediate cells which results from these metabolic processes (Fig. 7) is dependent on the phase of the menstrual cycle and the hormonal situation.

A mixed flora or a pure coccal flora is not necessarily associated with cytologic changes, but is, however, mainly seen in patients with abnormal conditions in the vagina.

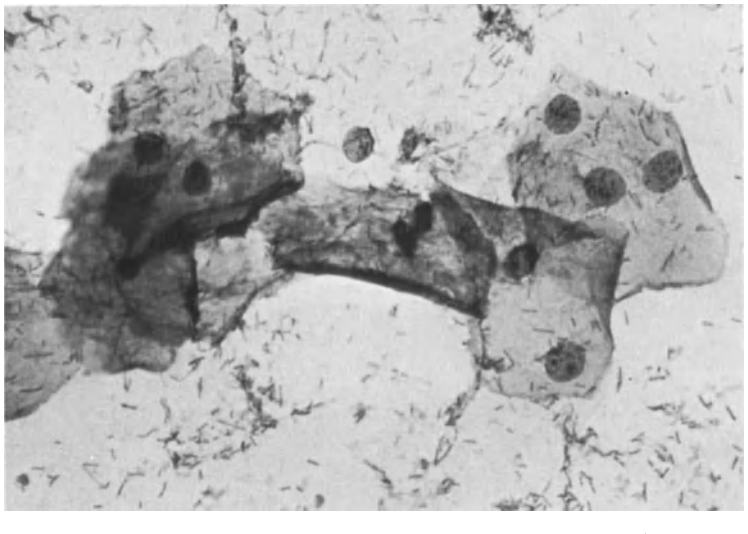

Fig. 7. Cytolysis due to Döderlein bacilli; a few isolated nuclei are present. × 40

III. Investigation of Hormonal Function

The investigation of hormonal function by cytologic studies is based on material collected from the lateral wall of the vagina. Exfoliated surface cells give useful information regarding the patient's hormonal state, since estrogens and progestogens leave characteristic traces in the squamous epithelium. The epithelium is built up and broken down in step with the menstrual cycle and can be regarded as a mirror of the endocrine state. The changes are sometimes referred to as the vaginal cycle. All sex hormones have a proliferative action on the squamous epithelium, but only the estrogens bring about its differentiation as far as the surface cell stage. Progestogens are necessary for the synthesis or deposition of glycogen in the squamous cell and are hence a prerequisite for cytolysis by Döderlein bacilli. During physiologic regeneration under hormonal control it is only the upper cell layers which are cast off and replaced by new cells. Up to the middle of the cycle there is an increasing tendency for isolated cells to appear in the smear. Surface cells with small pyknotic nuclei increase in numbers, and the proportion of large eosinophilic cells rises. From midcycle to the end of the luteal phase the changes go into reverse. During this part of the cycle the exfoliated cells tend to form clumps. Their cytoplasm is folded or rolled over at the edges. Bacterial cytolysis is most conspicuous at this time. On the basis of this and other features, several methods for cytologic evaluation of the hormonal state have been put forward (*Pundel* 1957; *Schmitt* 1953; *Soost* and *Baur* 1980; *Wied* 1953, 1973, 1976).

The hormonal state can be expressed by certain indices which are derived from various cytologic criteria. The most useful are the karyopyknosis index and the eosinophilia index. *Pundel*'s system summarizes the changes in the karyopyknosis index and the eosinophilia index during a normal 28-day cycle with maximum and minimum values correlated with the phase of the cycle. (A detailed account of the application of cytologic methods for hormonal diagnosis cannot be given here. The reader is referred to the appropriate literature: see above.) As compared with other methods for ascertaining the hormonal state, cytologic investigation is simple and inexpensive. Given technically satisfactory smears, it offers a high standard of diagnostic reliability.

F. Benign Changes

I. Inflammatory and Degenerative Changes

1. Pathophysiologic Principles

Inflammation is defined as the sum total of all the biochemical and morphological reactions of vascular connective tissue which can be evoked by noxious influences of various kinds. The pathogenesis of inflammatory changes is extremely complex. When they occur in the female genital system they are usually associated with some abnormality of the vaginal milieu.

The pathogens most frequently responsible for inflammatory reactions are staphylococci, streptococci, gonococci, *Escherichia coli, Trichomonas vaginalis, Candida*

albicans, herpesviruses, the condyloma virus of the papova group, *Leptothrix,* and *Hemophilus vaginalis.*

2. The Cytologic Picture

Inflammatory reactions affecting the vagina and cervix uteri are recognizable not only from the appearance of leukocytes and other such cells in the smear, but also by characteristic changes in the epithelial cells. As a result of increased metabolic activity and exposure to substances having cytotoxic effects, the morphological picture of the epithelium undergoes typical changes which are reflected in the staining behavior of the cytoplasm and in alterations in nuclear and cytoplasmic structures. Cells with an active metabolism usually have a basophilic cytoplasm, this appearance being due to the activity of their ribosomes. The open network of their chromatin pattern, together with the appearance of nucleoli, bears witness to the activity of their nuclei. If the increased metabolic demands continue for long periods, as may be the case in chronic inflammatory conditions, the cytoplasm assumes increasingly amphophilic staining characteristics. The nucleus shows so-called functional edema, and its structure tends to become indistinct. These changes are still reversible and if the cause of the inflammation is removed they will regress. Nevertheless, these appearances may be regarded as evidence that the individual cell has reached the limits of its powers of compensation, and if it is exposed to further stress irreversible biochemical lesions must be expected. These will be followed by regressive and degenerative changes. Such changes are characterized by vacuole formation in the cytoplasm resulting from dysionia or fatty degeneration (Fig. 8). In such cases the cytoplasm typically displays intense eosinophilic staining – the result of cessation of ribosomal activity, breakdown of RNA, and condensa-

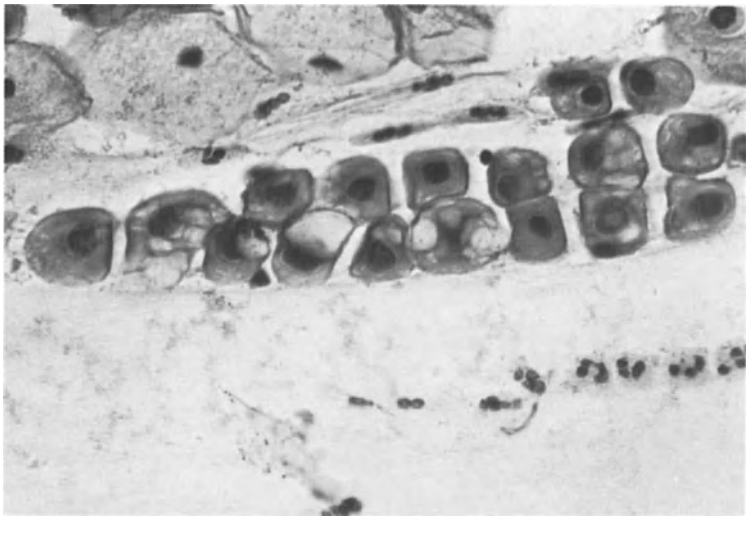

Fig. 8. In addition to surface cells, there are parabasal cells with inflammatory and degenerative changes including vacuole formation in the cytoplasm. x 40

tion of cytoplasmic structures. Finally, the cell loses the power of maintaining its shape, and the cytoplasm liquefies and disappears.

Degenerative changes in the nucleus present a variety of pictures, known by the terms karyolysis, karyorrhexis, and pyknosis (Fig. 9). Nuclear degeneration often begins by deposition of chromatin on the nuclear membrane, which gives the appearance of being thickened. The secretory cells of the endocervix are particularly sensitive to adverse influences. Under such conditions their cytoplasm is often reduced to a few threads. The bare nuclei of these secretory cells, together with the associated inflammatory and degenerative changes, may under some conditions cause diagnostic difficulties, especially if there are variations in nuclear size.

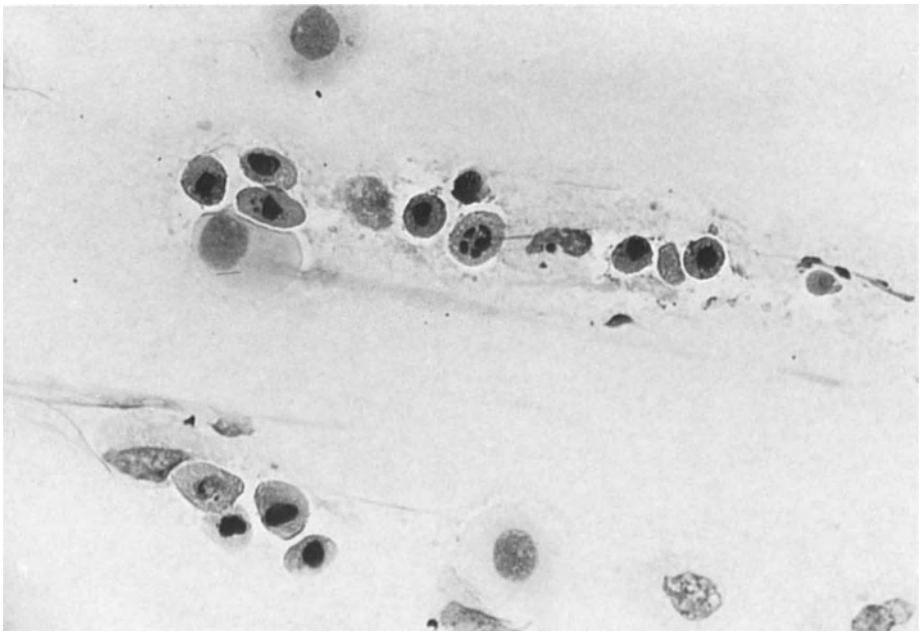

Fig. 9. Various types of nuclear degeneration in atrophic epithelial cells: karyorrhexis, karyolysis, pyknosis. × 40

Though the bacteria listed above are practically unidentifiable under the microscope and occur in clumps or masses in the smear, viruses can sometimes evoke characteristic epithelial changes. Herpesviruses produce cells with more than one nucleus (Fig. 10). The nuclei are closely packed together and tend to flatten one another where they are in contact, a phenomenon known as "nuclear molding." The interior of the nucleus has a striking "ground glass" appearance. Intranuclear inclusions are sometimes seen.

"Balloon cells" point to the presence of condylomata acuminata (Fig. 11), a condition caused by a virus of the papova group known as condyloma virus. One of the main features of these striking cells is the giant perinuclear halo which occupies almost

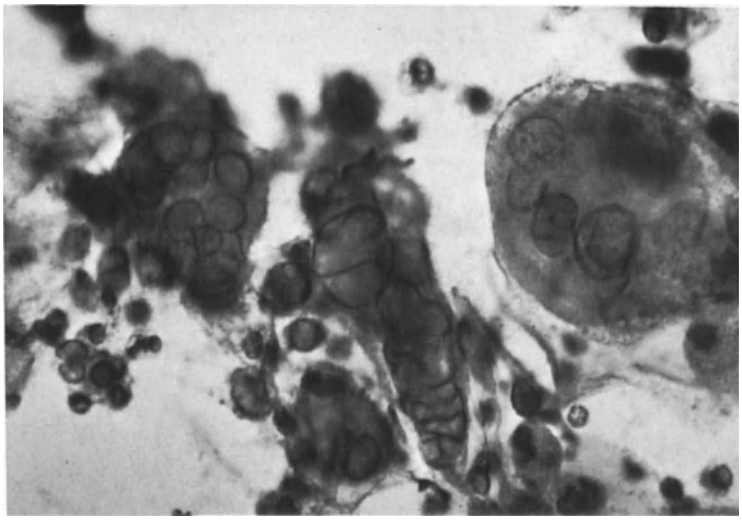

Fig. 10. Multinucleate cells in herpes virus infection: ground-glass structure, nuclear molding. x 63

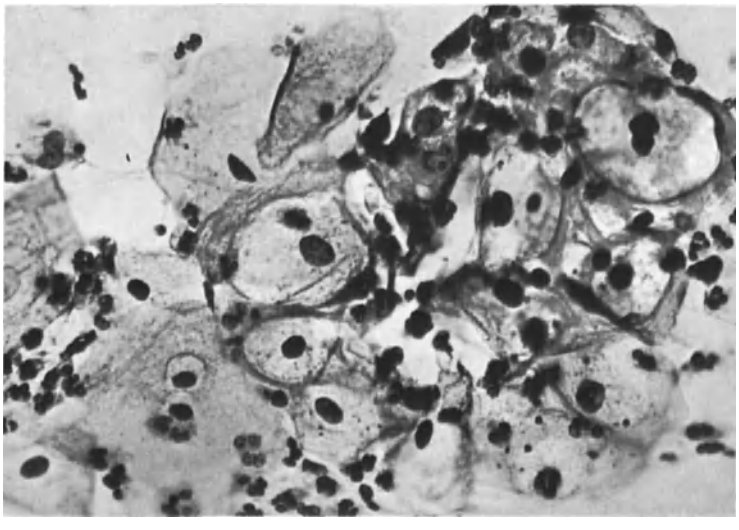

Fig. 11. Balloon cells in condylomata acuminata. x 40

the entire cell interior, leaving only a narrow, sharply demarcated, optically dense cytoplasmic border. The round or oval nucleus, usually hyperchromatic, lies within this optically empty space. Binucleate cells are common. These changes are designated as koilocytotic atypia.

Trichomonas vaginalis and *Candida albicans* can usually be identified directly. Narrow perinuclear haloes are particularly common in patients with trichomoniasis, but they are not pathognomonic of this infection (Figs. 12, 13).

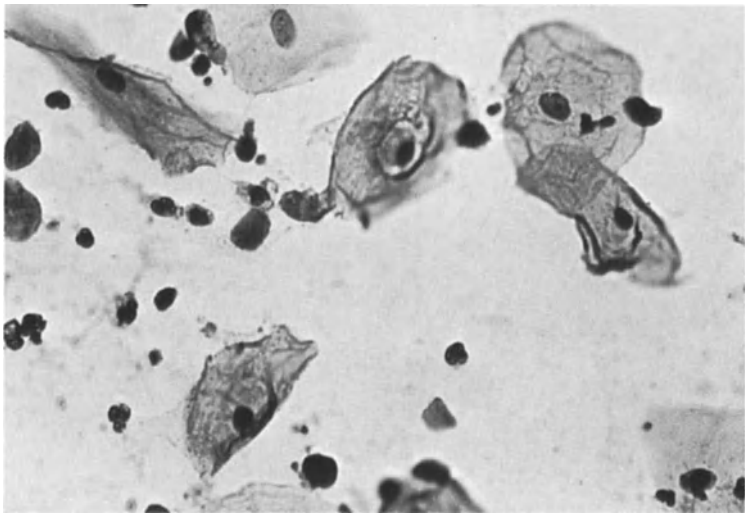

Fig. 12. *Trichomonas* infection, perinuclear spaces. x 40

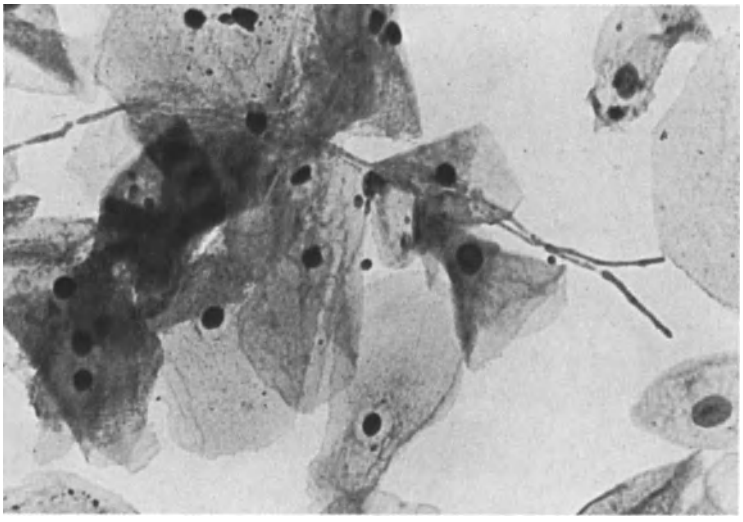

Fig. 13. Hyphae and spores in a case of infection by *Candida albicans.* x 40

The long unsegmented threads of *Leptothrix* (Fig. 14) are commonly seen in association with *T. vaginalis.* In such cases the inflammatory cell reaction is usually very conspicuous. Nuclear atypias are not uncommonly encountered in these circumstances, and may point to an etiologic connection between *Trichomonas* infection and carcinogenesis. However, the existence of this link is still disputed.

Infection with *Hemophilus vaginalis* is often evident from the presence of "clue cells." These are squamous epithelial cells coated by the thick layer of *H. vaginalis* (Fig. 15).

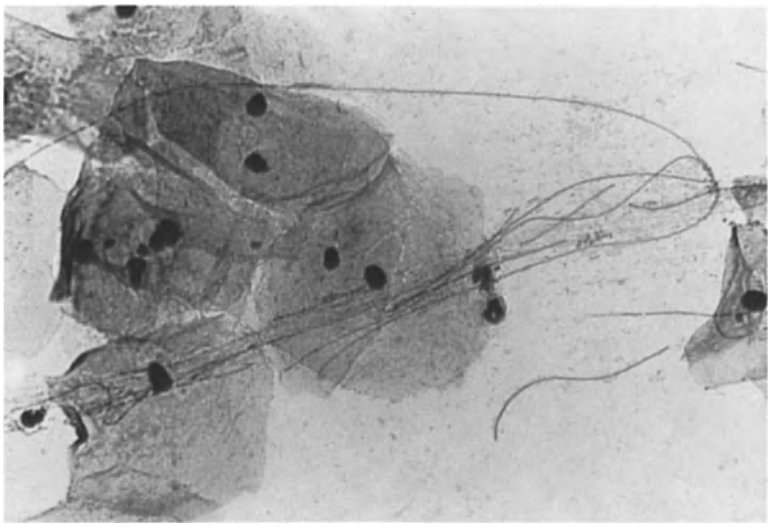

Fig. 14. *Leptothrix.* x 40

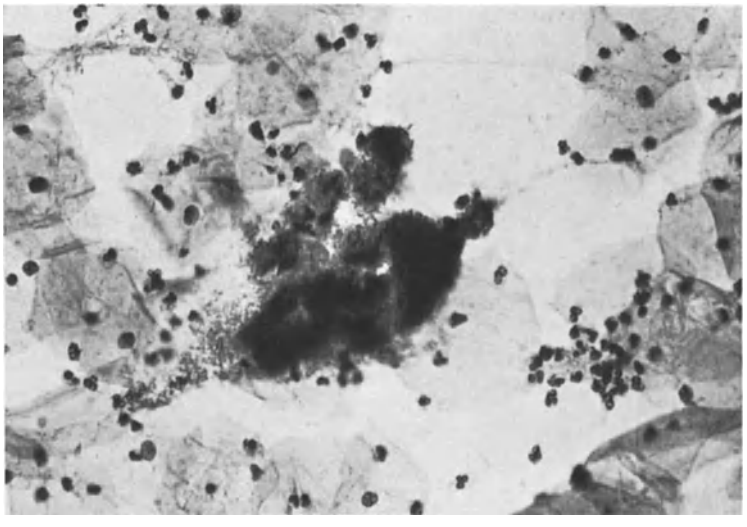

Fig. 15. Clue cells in infection with *Hemophilus vaginalis.* x 25

A special form of inflammatory lesion in the cervical canal is secondary lymphoid or follicular cervicitis. Cytologically, this condition is characterized by enormous numbers of lymphocytes at various stages of maturation together with plasma cells and histiocytes. As a rule, the cells lie separate from one another and do not form clumps (Fig. 16).

The cells known as large active histiocytes are likely to be seen in patients with chronic inflammatory conditions. Their function in the inflammatory process is to act as scavengers, whereas the small histiocytes are thought to be responsible for immuno-

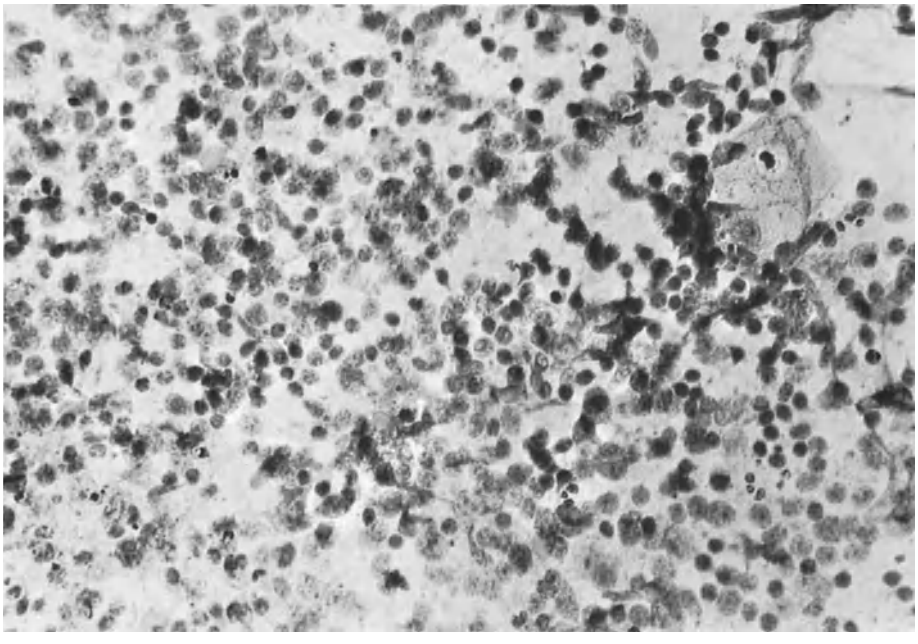

Fig. 16. Follicular cervicitis. × 25

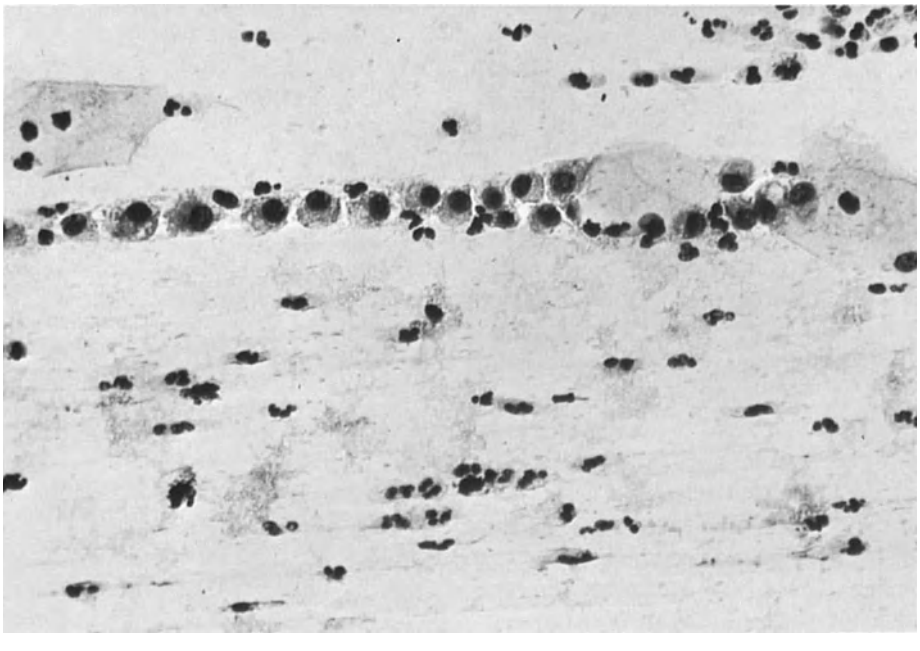

Fig. 17. Histiocytes, two surface cells. × 40

logic defense. The significance of histiocytic giant cells is not fully understood (Fig. 17).

Intraepithelial inclusions consisting of cell remnants or entire cell units – the so-called engulfments – are occasionally seen. This condition is known as pathologic phagocytosis. Engulfments are most commonly encountered in severe and protracted inflammatory conditions, frequently as a concomitant of malignant change.

The presence of multinucleate epithelial cells is another sign of chronic inflammation. They point to disordered mitotic activity and are also common in dysplasias, after irradiation, after cytostatic therapy, and as a result of folic acid deficiency. Differential diagnosis between these conditions calls for careful history taking.

II. Regeneration and Metaplasia

1. Pathophysiologic Principles

Like certain other tissues of the body, the squamous and glandular epithelia of the female genital tract are in a state of constant flux and renewal. This activity is centered upon the germinal layer. It is the source of continuous physiologic cell replacement: as the epithelial cells are exfoliated and undergo necrobiosis, new cells are produced from the germinative zones. This process is known as physiologic regeneration. In the squamous epithelial covering of the vagina and ectocervix there is a single layer of basal cells which constitutes the germinal layer. It is separated from the underlying stroma by the basement membrane. The generation cycle of basal cells is of 30 days' duration (*Stegner* 1973), but under certain conditions it may be considerably shorter (*Averette* et al. 1970). Above the basal cell layer there are three or four layers of parabasal cells (*Blaustein* 1977). They display intense mitotic activity. Under physiologic conditions, they have a generation time of 3 days (*Stegner* 1973), though in some circumstances this can be curtailed (*Averette* et al. 1970). The basal and parabasal cell layers form the germinative zones. Physiologic regeneration is confined to these layers.

Mitoses are found in the more superficial layers of cells only in cases of pathologic regeneration or in various forms of malignant proliferation (*Fettig* and *Oehlert* 1964; *Fettig* and *Sievers* 1966; *Fettig* 1970). The term "pathologic regeneration" is applied to repair processes, occurring, for example, after the epithelium has been damaged. Depending on the extent of the lesion, they may end either in complete restitution and replacement by cells identical to those originally present or in scar formation. Under physiologic conditions the cytologist expects to find nothing but endocervical cells and exfoliated postmitotic cells from the upper layers of the squamous epithelium, but when the integrity of the epithelial covering has been breached cells from the deeper layers will appear. They lie singly or in groups and are known as erosion cells. As repair begins the cytologist will encounter regeneration cells. Depending on the site of the lesion, they may be derived from the germinative zones of the squamous epithelium or from the corresponding layers in the epithelium of the endocervical glands. If the defect penetrates deeply into the tissues there may occasionally be mesenchymal cells, principally in the form of elongated spindle-shaped fibroblasts with centrally or marginally situated oval nuclei.

In the cervical canal regeneration takes place from the reserve cells. Under physiologic conditions their regeneration cycle takes considerably longer than that of basal cells (*Stegner* 1973). They appear only under pathologic conditions, namely when proliferation goes beyond the physiologic limits of regeneration (*Burghardt* 1972), and are not seen in the normal healthy epithelial lining of the endocervix, which consists of a single layer of tall, columnar, ciliated and mucus-secreting cells. For this reason there are various opinions regarding their histogenesis (see *Patten* 1969). Many authors classify them as epithelial cells (*Patten* 1969; *Reagan* and *Ng* 1973; *Stegner* 1973). Their appearance in cytologic smears has been regarded as evidence of reserve cell hyperplasia (*Patten* 1969).

It is a well-known fact that in women of child-bearing age the junction between squamous and glandular epithelium is often displaced distally, with the result that patches of glandular epithelium come to lie on the vaginal surface of the cervix, where they are exposed to various adverse influences. Theoretically, a breach in the epithelium at this junction could be repaired by cells from the squamous epithelium or the glandular epithelium. However, under such conditions, regeneration is not physiologic but pathologic and is characterized by proliferative activity going beyond the usual limits.

Electron microscopic studies (*Stegner* 1973) have shown that reserve cells, being resting germinative cells, are equipped with a full set of organelles which, in the event of normal development to a columnar cell, will multiply and increase. However, under certain conditions such as pathologically enhanced proliferation, they may even decrease. Such a decrease in the number of organelles in these cells can be regarded as ultrastructural evidence of proliferation in response to an irritant – the condition known as "ultrastructural metaplasia."

Though reserve cells become visible in microscopic preparations only in patients with enhanced proliferation – and can therefore be expected to have a diminished or modified set of organelles (*Stegner* 1973; *Ferenczy* 1977) – their detection can be regarded as an early morphologic sign of metaplasia. As a result of the proliferation-induced changes in their organelle equipment they can no longer develop into columnar cells, but only into cells which, electron microscopically at least, must be classified as squamous and which, as they mature, acquire all the light microscopic features of squamous epithelium. This process must therefore be interpreted as squamous metaplasia. However, squamous epithelium no longer possesses the highly specialized functions of secretory or ciliated columnar epithelium. In this instance metaplasia can therefore be defined as the conversion of a highly differentiated tissue. There is evidence of direct links between proliferation and differentiation and indeed the tendency of the cells to undergo elaborate differentiation is obviously in inverse proportion to their proliferative activity. As the phenomenon just described proceeds only via the germinal epithelium, it is termed "indirect squamous metaplasia."

As seen under the light microscope, the new cell communities in their immature state are by no means identical with the corresponding layers of healthy squamous epithelium. Histologically, they present the picture of confluent areas of metaplasia, the cells of which are linked to one another and to the proliferating squamous cells in the vicinity by so-called interanastomoses (*Ferenczy* 1977).

If the noxious factor is removed and this epithelium matures it is then no longer distinguishable from the original squamous epithelium. Viewed through the colposcope, the recently epithelialized area has the appearance of a "transformation zone" with occlusion of gland crypts and formation of Naboth's follicles.

Although metaplastic phenomena presuppose some disturbance of physiologic cell replacement, cells from areas of metaplasia are so commonly seen in smears from women of reproductive age that they cannot be regarded as abnormal.

2. The Cytologic Picture

Cells from regenerating epithelium are characterized by relatively large, "active" nuclei with one or several nucleoli and finely granular chromatin. The cells lie mainly in groups and have relatively pale cyanophilic cytoplasm which gives the impression of being semiliquid. If the breach in the epithelium is accompanied by moderate or severe inflammatory reactions the cytologist must expect to find the signs of inflammation described above. In such cases special care is needed to distinguish between regenerating epithelium and proliferating neoplastic cells (Fig. 18).

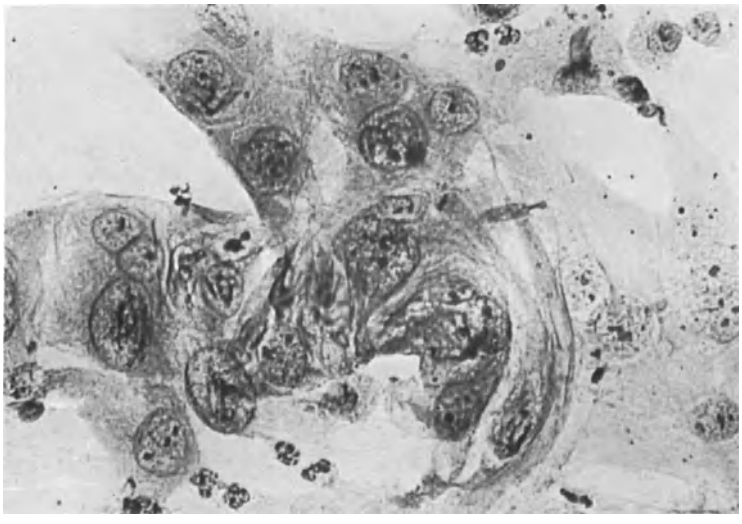

Fig. 18. Regenerating epithelium. × 40

Reserve cells are for the most part rounded in shape and have a centrally situated nucleus. Their chromatin structure is finely granular and shows no obvious areas of condensation which might be taken for nucleoli. Their cytoplasm is delicate and cyanophilic. They are smaller than basal cells (*Soost* and *Baur* 1980) and can best be recognized when they are still adherent to the deep surface of the columnar cells. When lying singly they can be confused with monocytes, histiocytes, or stroma cells.

Cells from areas of metaplasia display highly characteristic cytologic features (Fig. 19). The shape of a metaplastic cell is dependent on its degree of maturation. Immature cells are usually round or oval, but sometimes have irregular outlines and pointed cytoplasmic projections. The centrally situated nucleus is round and finely granular. It may show occasional chromocenters, but nucleoli are not present. As maturation advances the cells become more and more similar to cells from the corresponding layers of the original squamous epithelium. Before their maturation is finally completed the chief criterion which distinguishes them from normal squamous cells at the same stage of maturation is the fact that their cytoplasm is denser. In such cells it is possible to distinguish an inner zone of paler endoplasm from an outer zone of dark ectoplasm. The difference between the two zones gradually diminishes, but does not entirely disappear until the cells attain full maturity. By that stage their origin is no longer discernible. The cytoplasm of metaplastic cells stains intensely cyanophilic with pronounced accentuation at the cell margin, but in the presence of inflammatory or degenerative changes it may be amphophilic or eosinophilic. Whereas immature metaplastic cells usually lie in loose groups, maturing cells show an increasing tendency to a solitary arrangement and fully mature cells are invariably isolated.

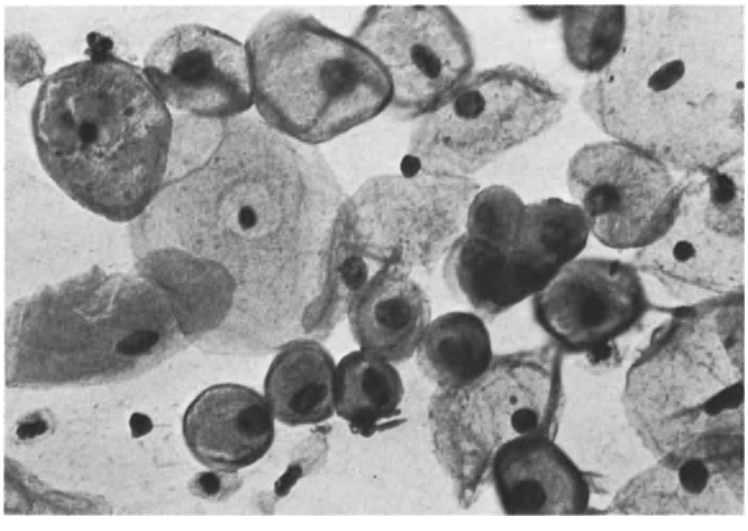

Fig. 19. Metaplastic cells at various stages of maturation. × 40

III. Atrophy

1. Pathophysiologic Principles

Atrophy is defined as an acquired decrease in cell size (simple atrophy) and/or a decrease in cell number (numerical atrophy) in a tissue. In the vagina and ectocervix such changes usually take the form of numerical atrophy. It is caused by lack of ovarian

hormones, which leads to reduced cell turnover and thinning of the cell layers. Only the basal and parabasal cell layers remain intact. Withdrawal of the hormonal stimulus from the germinative zones has two important consequences: firstly, the formation of an adequate protective layer above the deeper tissues comes to an end, and secondly the synthesis of glycogen in the intermediate cells ceases. This means that the biochemical barrier to pathogenic bacteria is lost and that the vagina and cervix become increasingly susceptible to harmful influences from outside the body. Because the production of lactic acid from glycogen is no longer adequate, the pH of the vagina shifts to the alkaline side of neutrality. This change in the local environment favors the onset of disease and explains the increased frequency of inflammatory and degenerative changes associated with atrophy. Hormone deficiency states of this kind are most frequently encountered in prepuberty and in the late postmenopause. However, patients belonging to the first of these categories are not included in cancer prevention programs and are seldom if ever encountered in the present context.

Because of the thinning of the cell layers the underlying stroma comes close to the surface, while its prominent vascular stromal papillae with their hairpin capillary loops are recognizable as red dots when viewed through the colposcope. In the presence of any pronounced inflammatory reaction the local circulatory abnormalities and the accompanying involvement of adjacent tissue cells make these changes even more conspicuous, and they may assume the typical macroscopic picture of granular colpitis. The distance which inflammatory products have to travel to reach the surface is now very short and their journey is further facilitated by the increasing permeability of the epithelial cell junctions. Furthermore, any trauma, even quite minor, can cause circumscribed hemorrhages. The outcome of these pathologic changes is visible in the smear.

2. The Cytologic Picture

Cytologically, the main feature of an atrophic smear is that it consists almost exclusively of parabasal cells. Mature squamous cells are absent. In the final summing up this cell picture is classified as grade 1 in *Schmitt*'s grading of hormone effects. The final stage is the outcome of gradual failure of ovarian function, usually developing over many years. During this time the cytologist may encounter every possible stage of decreasing epithelial proliferation. One special phenomenon is the "menopausal mixed picture" in which completely immature epithelial cells are seen side by side with intermediate cells and surface cells in all stages up to full maturity (Fig. 20). A completely atrophic smear is not usually to be expected until late in postmenopausal life.

It is a noteworthy fact that after surgical or radiologic destruction of ovarian function atrophic changes in the squamous epithelium develop much more rapidly than the corresponding changes due to the decline in ovarian function with advancing age.

For the reasons previously mentioned, the background of an atrophic smear is frequently characterized by debris, protein deposits of greater or lesser density, and inflammatory cells, usually poorly preserved. The poor preservation of the cells is due to the fact that the phenomena outlined above do not run an acute course but extend over a longer period, and the cellular components are therefore subject to autolysis.

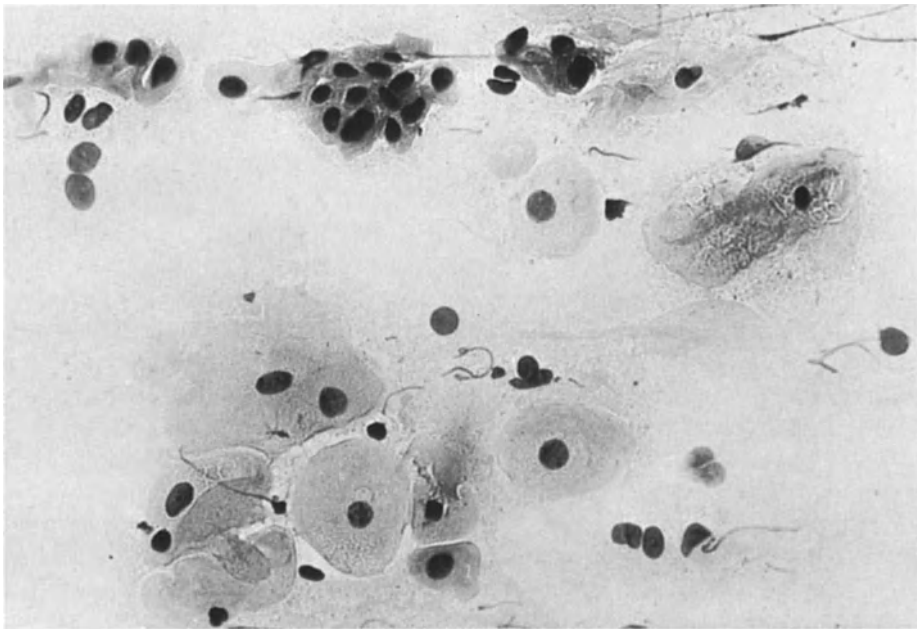

Fig. 20. The mixed picture seen at the menopause: surface cells, intermediate cells, parabasal cells, and bare nuclei. × 40

Another feature sometimes seen in atrophic smears is so-called inspissated mucus. This consists of rounded masses of thickened mucoid material. They frequently have an area of increased density in the center and are roughly the same size as parabasal cells. It is important to distinguish them from naked tumor cell nuclei.

Furthermore, the immature squamous cells often assume the form of "atrophic cell cohesions," which are two-dimensional groups without recognizable cell boundaries (Figs. 21, 22). They are also known by the term "pseudosyncytial clusters." As a result of degenerative changes, nuclear and cytoplasmic vacuoles are relatively common. The cells in the atrophic smear for the most part display amphophilic or eosinophilic staining.

Difficulties in differential diagnosis may be presented by certain small eosinophilic cells with pyknotic nuclei. They lie singly, vary in shape, and are probably produced by dehydration of the nucleus and cytoplasm with condensation and hyalinization of the latter (*Jenny* 1973).

Bare nuclei, often swollen, are often seen in the indistinct and dirty background of the smear. They may be derived from squamous cells or secretory cells. The origin of these nuclei is ascertainable only when better preserved cells of the same kind are present in their vicinity.

In other respects, the inflammatory, regressive, and degenerative changes in the squamous and secretory cells have the same cytologic features as those previously described. The end product of these processes is debris of variable density, in which only a few isolated cells are to be found. This state is most commonly seen in severe chronic senile vaginitis.

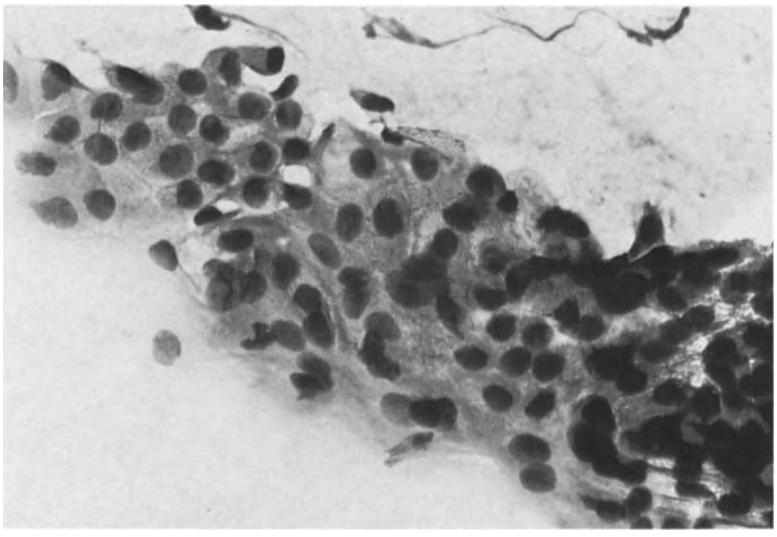

Fig. 21. Atrophic cell cohesions. x 40

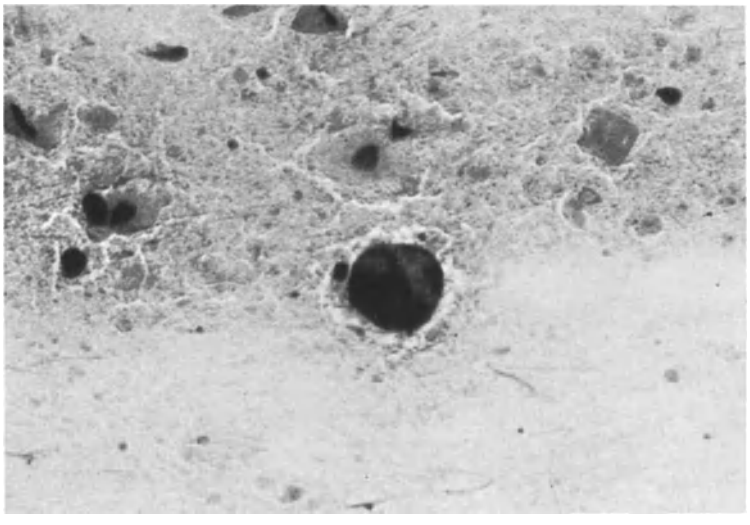

Fig. 22. Atrophic vaginitis: mainly cell debris, a few degenerating squamous cells, inspissated mucus. x 40

An atrophic smear can present diagnostic problems when dysplastic or atypical cells are mixed with necrotic cell material. To ensure a trustworthy cytologic report it is necessary to repeat the smear, preferably after local, parenteral or oral application of estrogen, unless the presence of unequivocally abnormal cells demands immediate biopsy and histologic examination. Within a few days after application of estrogen the atrophic squamous epithelium will have undergone complete reconstruction and the

smear background will become clean. We recommend daily topical application of estriol ointments or vaginal pessaries for 5–7 days, the total dosage being 1 mg estriol. A repeat smear is taken 4–5 days after the end of the course of treatment. Dysplastic and abnormal cells do not react to treatment with estrogen and are easily identifiable in the repeat smear.

IV. Keratinization

1. Pathophysiologic Principles

The vagina and ectocervix are clothed with nonkeratinizing squamous epithelium having an organized structure. However, in the more mature cells electron microscopy has revealed keratinosomes as a source of protein-bound keratin precursors (*Ferenczy* 1977). They hence possess the potential for producing keratin. Nevertheless, keratinization at these sites takes place only under pathologic conditions. Although its causes are by no means uniform, it is clear that in every instance its purpose is to protect the underyling tissues (*Ferenczy* 1977). Diffuse keratinization most commonly develops as a result of chronic irritation, e.g., in association with uterine prolapse. Circumscribed areas of keratinization may be seen in women who wear pessaries. No systemic conditions which predispose to keratinization are known. Macroscopically and colposcopically, keratinization presents as diffuse or circumscribed leukoplakia.

The presence of a horny layer consisting of scales devoid of nuclei is known as hyperkeratosis. The condition termed "parakeratosis" is another form of keratinization. It consists of one or several layers of relatively small squamous cells covering the surface. They have dark pyknotic nuclei. Parakeratosis is regarded as an abnormality of differentiation involving nonkeratinizing squamous epithelium with premature but incomplete keratinization (*Stegner* 1973).

It is important to differentiate between leukoplakia and the rare proliferative forms of condyloma acuminatum, which are also accompanied by keratinization in the surface layers.

2. The Cytologic Picture

Cytologically, keratinization, here designated as "hyperkeratosis" (Fig. 23), is characterized by the occurrence of non-nucleated polygonal eosinophilic or orangeophilic scales. A feature seldom seen in smears is the "keratin pearl," a rounded epithelial mass with a concentric, onion-skin structure. The cytologic features of parakeratosis are small polygonal cells, which may even be spindle-shaped when seen in profile (Fig. 24). They have a small hyperchromatic nucleus and the staining of their cytoplasm is eosinophilic or orangeophilic. They are also known as miniature surface cells.

The cytologist should not regard the occurrence of these cells as evidence of any serious pathologic abnormality, provided that no dysplastic or abnormal cells are to be found. However, it must always be borne in mind that malignant changes can hide themselves among areas of leukoplakia, and for this reason a repeat smear made with a

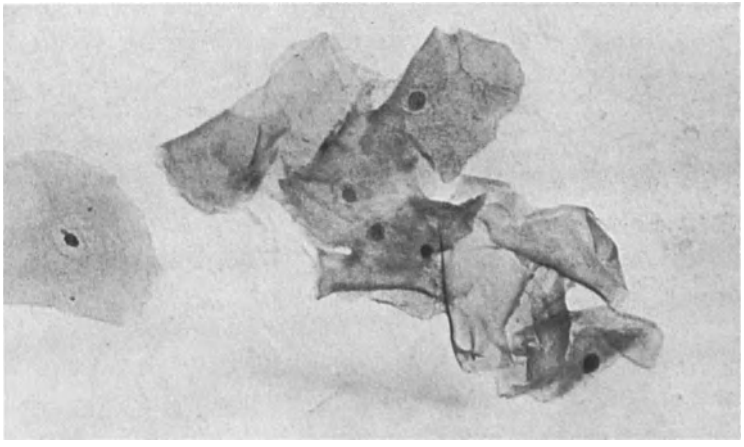

Fig. 23. Hyperkeratosis. In addition to surface cells there are keratin scales, a few having "ghost nuclei." x 40

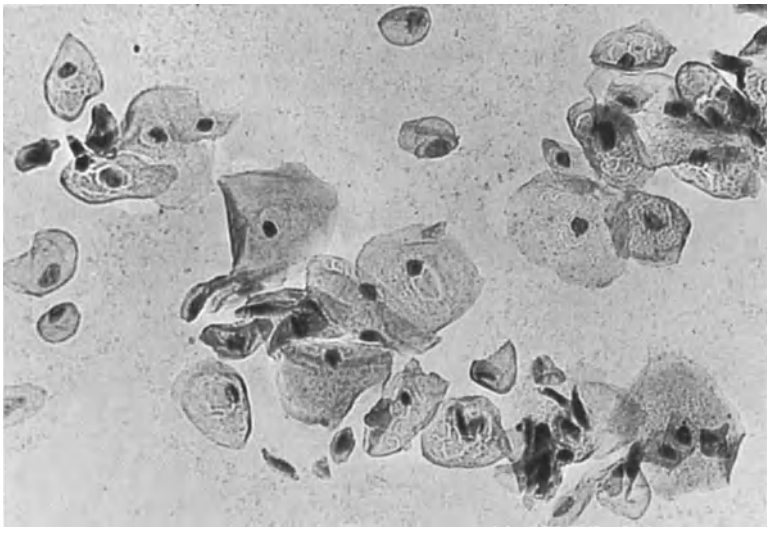

Fig. 24. Parakeratosis. Besides the surface and intermediate cells, there are small polygonal or spindle-shaped cells, most of which have chromatin-dense pyknotic nuclei. Some of the cells lie on top of one another. x 40

spatula should be requested whenever the first smear is not unequivocally negative. The repeat smear will usually enable the cytologist to distinguish between the various lesions which are associated with keratinization. This applies in particular to condylomata acuminata, keratinizing dysplasias, and keratinizing squamous carcinoma.

F. The Cytologic Features of Atypia

In principle, the discrimination between abnormal and normal cells is based upon changes in the nucleus and cytoplasm visible under the light microscope. However, in the final assessment of a smear the cytologist makes use of further criteria, some of which may be of great diagnostic value. Among these are the smear background, the arrangement of the cells, their numbers, and their pattern of distribution. As there is no single hallmark characteristic of every cell from a given lesion, not too much weight should be placed upon the appearances of an individual cell. This means that every cytologic diagnosis must be based on the sum total of the cytologic criteria.

The principal characteristics of atypia are the nuclear abnormalities. Apart from nuclear enlargement, the most important of these is hyperchromasia. It is due to the increased chromatin content of the nuclei, which results from their increased aneuploid chromosome complement, this being due to the fact that tumour cells commonly deviate from the diploid or tetraploid chromosome complement of normal cells. The staining of this increased quantity of chromatin creates the impression of hyperchromasia. However, by no means all tumors have an increased chromatin content. Furthermore, it should be remembered that the impression of hyperchromasia depends on two factors, namely nuclear volume and chromatin content. A nucleus with a normal chromatin content will appear hyperchromatic if it is shrunk but hypochromatic if it is enlarged; in other words the impression of hyperchromasia or hypochromasia is to some extent determined by degenerative changes. From this it follows that the two phenomena must be considered in conjunction if they are to be properly evaluated. As a rule, however, pyknotic nuclei from tumor cells are larger than pyknotic nuclei from healthy epithelial cells, and enlarged nuclei from tumor cells are generally hyperchromic as compared with nuclei from normal cells. As will be understood, these criteria cannot be used to identify tumor cells with a normal chromosome complement.

A shift in the nuclear-cytoplasmic ratio in favor of the nucleus is another trustworthy diagnostic criterion of atypia. Further important diagnostic points include nuclear polymorphism or anisokaryosis – an appearance produced by variations in chromatin content, the degree of chromatin disaggregation, and the effect of degeneration. The chromatin pattern of abnormal nuclei diverges very obviously from that of the chromatin network of normal nuclei and can therefore be utilized for diagnosis. The distribution of the chromatin may be regular or irregular, and it may form large masses or fine granules. Band-shaped structures are occasionally seen. They are said to be more frequent in adenocarcinoma of the cervix (*Reagan* 1971). Evidence of augmented cellular activity may be given by the nucleoli. They are single or sometimes multiple and present as areas of chromatin condensation of varying size. Strikingly conspicuous are macronucleoli. They stain reddish, often appearing as rounded objects in the interior of the nucleus. They are especially frequent in adenocarcinomas. Multinucleate cells and mitoses are of little importance in the cytologic diagnosis of malignancy. Cytoplasmic changes should carry weight with the cytologist only if they are associated with nuclear abnormalities. However, the state of preservation of the cytoplasm and the sharpness of its outer margin are points of importance in the diagnosis of various other diseases.

Polymorphic cells are given special names based on their characteristic shapes – spindle cells, spider cells, fiber cells, and tadpole cells. They are most commonly encountered in patients with keratinizing squamous cell carcinomas. The arrangement of the cells can also provide valuable diagnostic evidence. For example, it is important to discriminate syncytial clusters from loose cell groups and from predominantly isolated cell patterns. Special forms of cell architecture such as rosettes or papillary structures can also be of diagnostic use. The staining reactions of the cytoplasm provide further pointers. Whereas cells from areas of keratinizing dysplasia and from keratinizing squamous carcinomas tend to be eosinophilic or orangeophilic, the cytoplasm of cells from areas of nonkeratinizing intraepithelial lesions and nonkeratinizing squamous cell carcinomas tends to be cyanophilic. As a result of premature degenerative changes in the cytoplasm, bare nuclei of bizarre shapes are commonly encountered in cases of undifferentiated squamous cell carcinoma.

Lastly, the smear background may contribute something to the diagnosis. In consequence of erosion of vessels by the tumor, the cytologist often sees old, broken down blood corpuscles side by side with well-preserved erythrocytes. When tissue destruction is occurring, Döderlein's bacilli are usually replaced by cocci or other bacteria. As a rule, the growth of a neoplasm is accompanied by inflammatory changes.

G. Dysplasias and Carcinoma In Situ

I. Definition, Etiology, and Pathogenesis

Dysplasia may be regarded as the outward sign of heteroplastic changes in squamous or metaplastic epithelium and can be defined as a disruption of the normal synchronism between nuclear and cytoplasmic maturation. Cytomorphologically, this is manifest in certain structural abnormalities in the nucleus and in anomalies in the maturation of the nucleus and cytoplasm. Its causes are multifactorial and can be divided into endogenous and exogenous influences. Among the endogenous influences are various factors, some specific to the individual, some sex linked, and others specific to the organ or tissue. Dysplastic changes can be caused by metabolic disorders provoked by local infections, cytotoxins, irradiation, and other harmful influences. However, from the appearance of the individual cell it is impossible to say whether its morphological anomalies have been caused by specific or nonspecific factors. There are in fact various diseases, differing in etiology, pathogenesis, and prognosis, but producing similar or identical cytologic changes, all of which come under the heading of dysplasia. Only in a proportion of cases is the cytologist dealing with precancerous changes in the narrow sense of the term. In order to discriminate between the various lesions the patient's history is not enough: the cytologist also requires an array of subtle morphological criteria.

Modern cytologic techniques are capable of detecting morphological anomalies in their early stages, provided that the technique used for collecting material is satisfactory. The cytologist can identify precancerous changes – in the narrow sense of the term – occurring in the "latent period" before the actual emergence of a malignant neoplasm. Invasive carcinomas can thus be prevented. This is the basic thinking on which the whole edifice of cancer prevention in gynecology has been built.

Follow-up studies have shown that mild, moderate, and severe dysplasia and carcinoma in situ can be regarded as stages in the progress of one and the same disease (*Richart* and *Barron* 1969). However, there is good evidence for the idea that carcinoma in situ is not always a sequela of dysplasia, but a separate and independent disease. It is a highly significant fact that, when dysplasia and carcinoma in situ coincide in the same patient, the dysplastic lesions are invariably situated distal to the areas of carcinoma in situ and indeed form a focal or multicentric lesion, whereas carcinoma in situ is believed to develop chiefly in the gland areas of the endocervix and to be derived from so-called abnormal metaplastic cells (*Burghardt* 1972). Certain authors (*Ferenczy* 1977; *Koss* 1968; *Richart* 1967, 1969, 1973) have attempted to reconcile these opposing views on the histogenesis of squamous cell carcinoma and the anomalies which precede it by lumping all precancerous changes, including severe dysplasia and carcinoma in situ, under the heading of CIN (cervical intraepithelial neoplasia), which is divided into three grades of severity. In this classification, squamous cell carcinoma is still regarded as the end stage of increasingly severe abnormalities in the squamous epithelium.

Richart and *Barron* (1969) carried out extensive follow-up studies of dysplasia and concluded that the progression times are as follows:

1. Mild dysplasia to carcinoma in situ 86 months;
2. Moderate dysplasia to carcinoma in situ 48 months;
3. Severe dysplasia to carcinoma in situ 12 months.

They believe that 80% of all forms of dysplasia will progress to carcinoma in situ within 10 years, unless this development is stopped by surgery.

Estimates of regression and progression rates given in the literature are widely discordant. In our own patients we found that 61% of mild and moderate dysplasias regressed, while 9% progressed to carcinoma in situ (*Sander* et al. 1978). Approximately 60% (*Boyes* et al. 1963) to 70% (*Kottmeier* 1961) of all carcinomas in situ are believed to develop into invasive carcinomas, the change occurring within a period of many years (5–15 years, *Soost* 1974; 13–20 years, *Boyes* et al. 1962).

Whereas mild dysplasias are to a great extent reversible, severe dysplasias and carcinoma in situ must be regarded as inevitable precursors of squamous carcinoma.

It is a fact that dysplastic changes can develop directly into squamous cell carcinoma without going through the sequence of grades of increasing severity, and there are also certain de novo cases of carcinoma. In some instances, at least, these facts can be explained by a discrepancy between the frequency of cytologic examination and the activity of promoter effects during the "latent period" of carcinogenesis.

II. The Cytologic Picture

Cytologically, dysplasia can be classified as follows:

1. According to grade: mild, moderate, or severe dysplasia;
2. According to the origin of the cells: nonmetaplastic or metaplastic;
3. According to the maturity of the cytoplasm: keratinizing or nonkeratinizing.

In cases of mild dysplasia one generally finds abnormal cells in the surface layers of the squamous or metaplastic epithelium; in moderate dysplasia, in the intermediate

layers of the epithelium; and in severe dysplasia or carcinoma in situ, in the deep layer (Figs. 25–28).

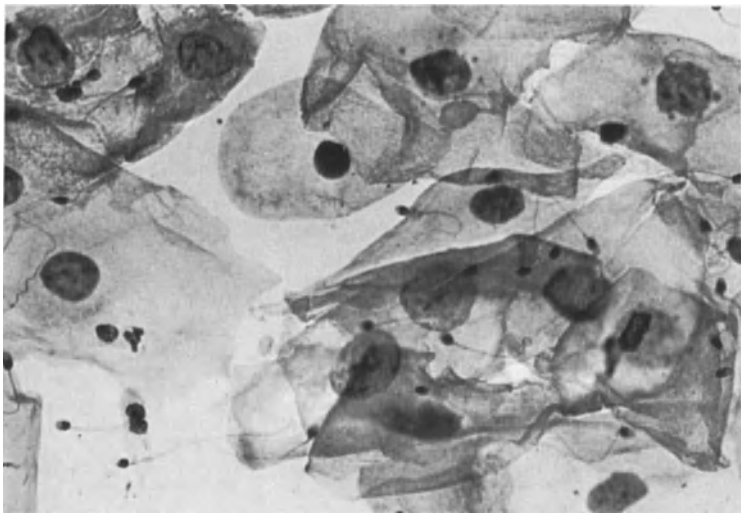

Fig. 25. Mild dysplasia: cells from the upper layers of squamous epithelium. The nuclear-cytoplasmic ratio is shifted in favor of the nucleus, and the chromatin structure is coarsened. x 63

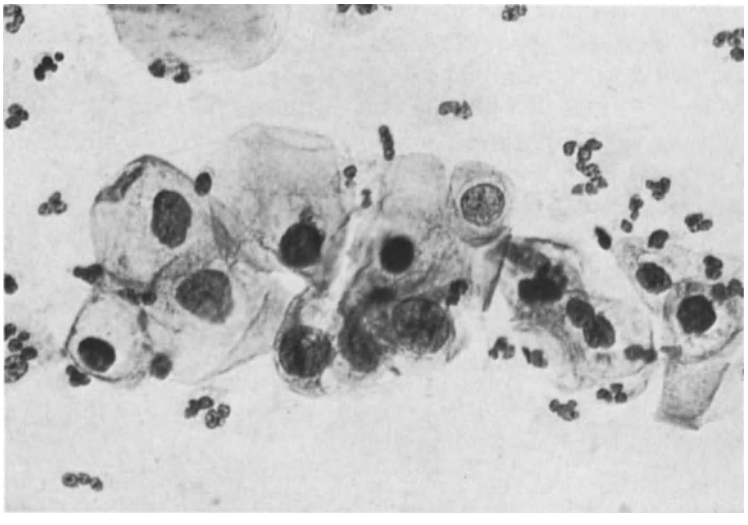

Fig. 26. Moderate dysplasia. Dyskaryosis of the upper and middle layers of squamous cells. x 40

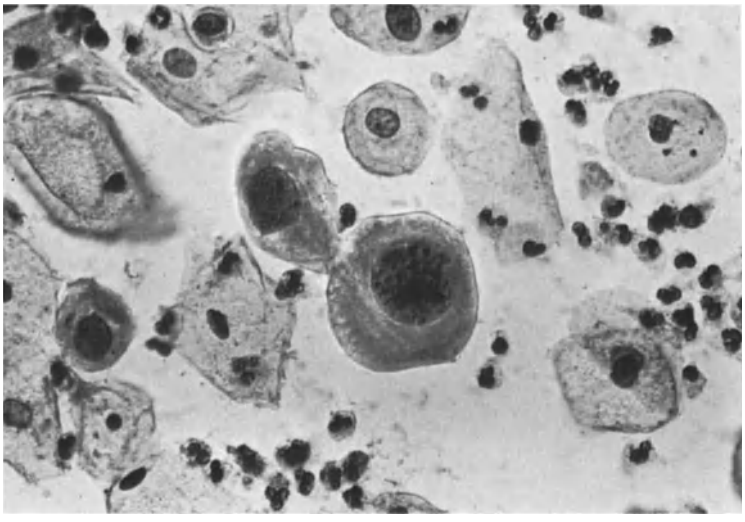

Fig. 27. Metaplastic dysplasia. Dyskaryotic changes in metaplastic cells which have a distinct ectoplasm and endoplasm. × 40

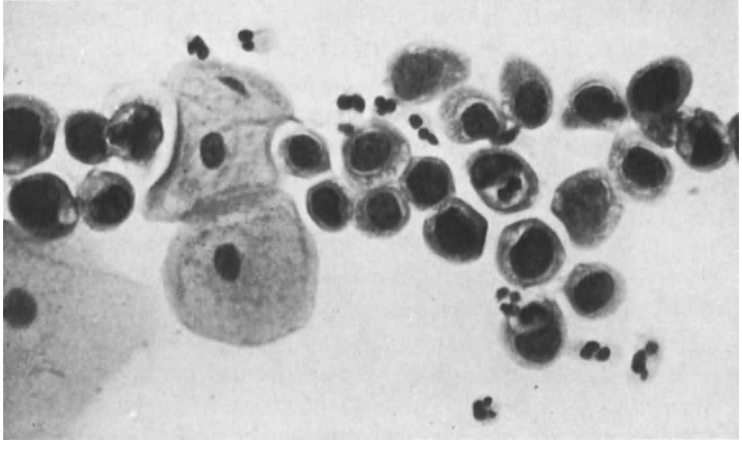

Fig. 28. Carcinoma in situ. Inflammatory and degenerative changes, cytoplasmic vacuoles, engulfments. × 40

Common to all forms of dysplastic change, including carcinoma in situ, are the structural abnormalities and hyperchromasia of the nucleus and the shift in nuclear-cytoplasmic ratio. The greater the severity of the disease, the more obvious and pronounced are these features. The cytologist uses this fact, together with a range of characteristic abnormalities, to allot the cells to their place among the different forms of dysplasia outlined above. All these details are then assembled in the final synopsis.

Within certain limits the number of abnormal cells in a smear can serve as an additional guide to the severity of the lesion. The more severe the dysplasia, the greater is

the number of exfoliated abnormal cells. This is due to their shortened generation time and their higher desquamation rate (*Ferenczy* 1977; *Patten* 1969). Furthermore, the number of abnormal cells rises as the surface area of the dysplastic lesions extends – and such lesions may be single or multicentric. In squamous epithelium, cell size diminishes as the dysplastic lesion becomes more severe, while the nuclear–cytoplasmic ratio moves in favor of the nucleus. The following details illustrate this tendency and emphasize certain important criteria for distinguishing between dysplasia and carcinoma in situ.

In dysplasia the average value for relative nuclear area is 16%, while in carcinoma in situ it is 30.5%. About 53% of all dysplasia cells are polygonal, but only about 8% of the cells from carcinoma in situ. In the average case of dysplasia, round cell and oval cells each make up only 21% of the total, whereas among the cells from carcinoma in situ 53% are round and 31% oval (*Koss* 1968; *Patten* 1969, 1973, 1976). Cells from areas of dysplasia, like cells from a carcinoma in situ, almost always lie singly, but in most cases of carcinoma in situ the individual cells are arranged in a characteristic streak or linear pattern.

Whereas dysplastic lesions usually show a polymorphic cell picture, especially if there is any tendency to keratinization, smears from cases of carcinoma in situ tend to be more monotonous and show only faint suggestions of differentiation.

As has already been pointed out, when dealing with atrophic smears it is very difficult to distinguish between carcinoma in situ and dysplasia or to grade the latter into mild, moderate, and severe forms. This difficulty arises from the fact that the epithelium is of insufficient thickness and identification of the different cell layers is hence impracticable. Such cases can be clarified by a short course of hormonal treatment followed by repetition of the smear. Atrophic epithelium reacts very rapidly to estrogens and regains its former thickness within a week or so, whereas dysplastic or abnormal cells respond feebly or not at all to hormonal stimulation.

Differential diagnosis between severe keratinizing dysplasia and keratinizing squamous cell carcinoma can be extremely difficult, because the general criteria outlined above are not fully applicable to these conditions and they are both characterized by the occurrence of conspicuously polymorphic cells such as fiber cells, spindle cells, spider cells, and tadpole cells. Nevertheless, these anomalous forms are less frequent in cases of dysplasia (approx. 15% of all cells), while they are often extremely obvious and striking in cases of keratinizing squamous cell carcinoma. Further guidance can be obtained from differences in chromatin structure: in dysplasia it tends to be more finely granular, while in carcinoma it is frequently coarse. Furthermore, dysplastic cells are often multinucleate (up to 5%), but carcinoma cells seldom show this abnormality. In cases of carcinoma the smear background tends to be "dirty," but in smears from dysplastic lesions it is predominantly clean.

There is also some risk of confusion between mild keratinizing dysplasia and the cells from condylomata acuminata. However, the latter are characterized by large, centrally situated, optically empty spaces (halos) containing the nucleus, which is usually slightly hyperchromatic (koilocytotic atypia). Multinucleate cells and "nuclear molding" are frequently seen. A further point is the common occurrence of cells which display these features but have basophilic cytoplasm, a point strongly against the diagnosis of keratinizing dysplasia.

The distinction between severe dysplasia and carcinoma in situ can sometimes be a problem, but in practice it is a decision which the cytologist should not attempt to make. Cytologically, it is usually impracticable to distinguish severe dysplasia or carcinoma in situ from microinvasion of tumor cells spreading into the underlying stroma.

H. Carcinoma of the Cervix

The varieties of primary carcinoma which arise in the cervix uteri are squamous carcinoma, adenocarcinoma, and mixed tumors, though squamous carcinoma is by far the commonest (*Abell* 1973; *Eder* 1975; *Ferenczy* 1977; *Koss* 1968; *Kraus* 1977; *Masubuchi* in *Wied* et al. 1976; *Novak* and *Woodruff* 1974). Secondary carcinomas do occasionally occur at this site, mainly as metastases from primary adenocarcinomas situated elsewhere. The peak incidence of squamous carcinoma is from 50 to 60 years of age (*Eder* 1975; *Ferenczy* 1977; *Soost* et al. 1979), whereas over half the cases of primary adenocarcinoma of the cervix occur after the menopause (*Reagan* and *Ng* 1973).

In the WHO nomenclature these tumors are classified according to their histologic characteristics into keratinizing squamous carcinomas, large cell nonkeratinizing, and small cell nonkeratinizing forms. Given well-preserved material, the cytologist can classify neoplasms along these lines. However, histologically and cytologically, transitional forms are frequent.

Smears from cases of squamous cell carcinoma contain abnormal cells which for the most part are well preserved and display striking variation in shape. These polymorphic cells are given descriptive names such as spindle cells, tadpole cells, fiber cells, or spider cells. Tonofilaments are sometimes seen, especially in elongated cells. Multinucleate cells are occasionally encountered (*Koss* 1968; *Patten* 1969; *Reagan* and *Ng* 1973). Neoplastic cells mostly lie singly; only in about 13% of cases do they form aggregates (*Patten* 1969, 1973, 1976). Their cytoplasmic border is usually wider than is the case in cells from less well-differentiated squamous carcinoma; as a rule it stains orangeophil or eosinophil and it is usually very dense and sharply demarcated. The nuclei are hyperchromatic and are coarsely granular in almost 60% of cases. In the vast majority of cells the chromatin is irregularly distributed. Macronucleoli are occasionally seen. As the result of degenerative changes, the nuclei frequently present as structureless, chromatin-dense, dark black objects with irregular outlines.

Large cell nonkeratinizing squamous carcinomas generally shed cyanophilic staining cells (*Soost* and *Baur* 1980). In roughly 23% of all cases the cytologist will encounter syncytial groups of tumor cells. The formation of syncytia is hence twice as frequent as it is in keratinizing squamous carcinoma. Cellular and nuclear polymorphism is seen in these cases too, but is largely confined to variations in cell and nuclear size; the cells do not display the extreme variety of shapes seen in keratinizing squamous carcinoma. In up to approximately 75% (*Patten* 1969; *Soost* and *Baur* 1980) the hyperchromatic nuclei have an irregular and coarsely granular chromatin pattern. Enlarged nucleoli are seen in a proportion of the nuclei. In most cases the smear background is dirty.

Smears from cases of small cell nonkeratinizing squamous carcinomas are distinguished by a predominance of relatively uniform, small, cyanophilic cells with a pro-

nounced shift in nuclear–cytoplasmic ratio in favor of the nucleus. Most of them lie singly and their cytoplasm is frequently autolyzed, so that the smears often contain numerous bare nuclei, usually round or oval in shape, though sometimes compressed and triangular. They are hyperchromatic and up to 80% have a coarsely granular pattern. In many instances they display one or more areas of chromatin condensation of various sizes and shapes; enlarged nucleoli are also common. The smear background is nearly always dirty.

Adenocarcinoma of the cervix is relatively uncommon and its differentiation from nonkeratinizing squamous carcinoma on the one hand and from endometrial carcinoma on the other can present difficulties. In contrast to smears from endometrial carcinoma, smears from such cases usually display an abundance of cells. The neoplastic cells may lie singly or in groups. In the latter case, they usually have a "side-by-side" arrangement (*Reagan* and *Ng* 1973). The vast majority show eosinophilic cytoplasmic staining. In addition, the cytoplasm is usually finely granular and may, though less commonly, contain minute vacuoles. The nuclei are round or oval and generally finely granular. They may show "chromatin bands" (*Reagan* and *Ng* 1973). Hyperchromasia is seen in approximately half of all such nuclei and becomes more frequent as dedifferentiation advances. Nucleoli – generally enlarged – are present in the majority of such neoplastic cells. The smear background is nearly always dirty. Cytologically, it is not easy to subdivide endocervical adenocarcinomas into well-differentiated and poorly differentiated forms. Such a distinction is based on relatively scanty cytometric data (Table 5; Figs. 29, 30, 31).

The presence of squamous carcinoma cells – mingled with the adenocarcinoma cells or lying separately – points to the existence of a mixed carcinoma. Smears from adeno-

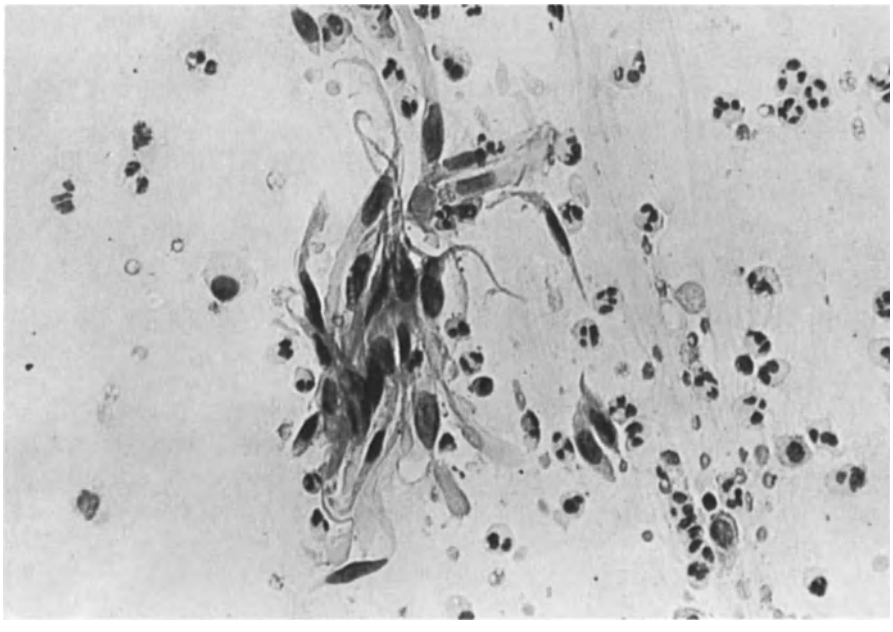

Fig. 29. Keratinizing squamous carcinoma: spindle cells, tadpole cells, and fiber cells. x 40

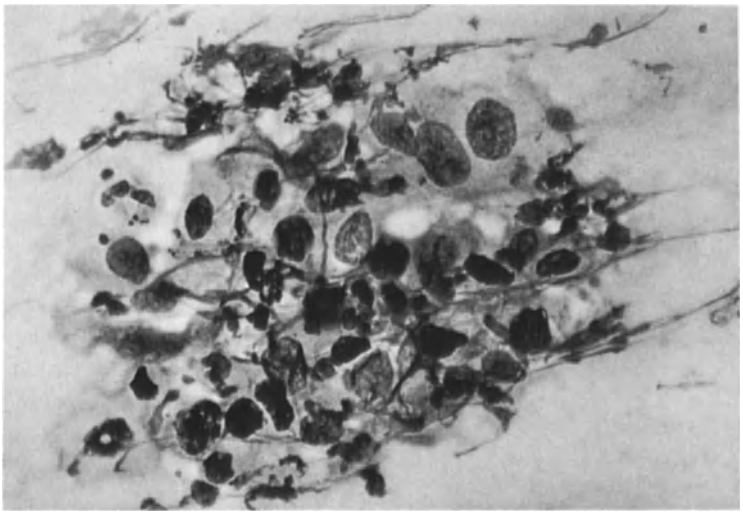

Fig. 30. Nonkeratinizing squamous carcinoma. Polymorphism of cells and nuclei, occasional nucleoli, dirty background. × 40

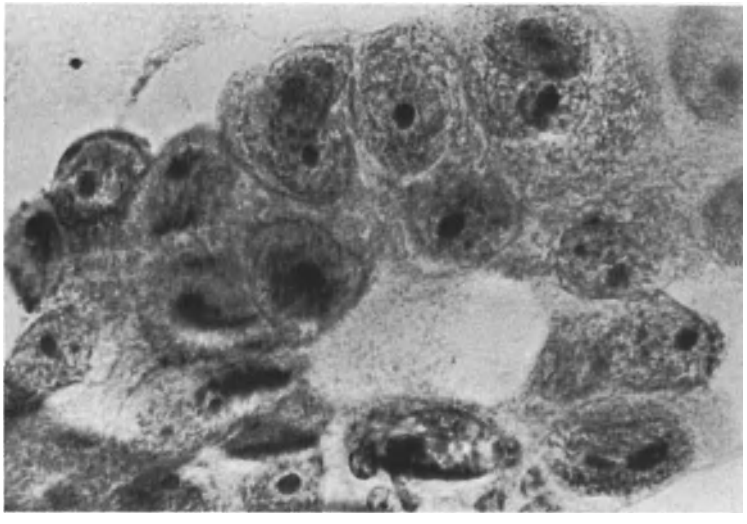

Fig. 31. Adenocarcinoma of cervix. Macronucleoli, side-by-side arrangement. × 63

acanthomas contain a proportion of metaplastic cells, but the diagnosis cannot be made by the cytologist because it is impossible to identify the site of origin of the cells. Adenocarcinoma of the cervix is frequently associated with carcinoma in situ of the squamous epithelium (*Reagan* and *Ng* 1973).

"Mesonephroid" carcinoma can be recognized only rarely and with difficulty. Also problematic as regards diagnosis are cells from adenocarcinomas in situ of the endocervix. Metastatic carcinomas can be detected cytologically, but only in occasional instances is it possible to identify their site of origin.

Cytologic criteria used in differential diagnosis are listed in Tables 2–4.

Table 2. Criteria for the diagnosis of dysplasia and carcinoma in situ (adapted from *Koss* 1968; *Patten* 1973, 1976)

Criteria	Nonkeratinizing dysplasia	Keratinizing dysplasia	Metaplastic dysplasia	Ca in situ
Cell area (μm^2)	1264 ± 201	1045 ± 408	492 ± 109	381 ± 112
Nuclear area (μm^2)	178 ± 32	169 ± 42	156 ± 35	116 ± 26
Relative nuclear area (%)	14	16.2	31.7	30.5
Cell arrangement (%)				
Isolated	89.6	80.7	73.3	87
Aggregates	10.4	19.3	26.7	13
Cell configuration (%)				
Polygonal	∿93	∿63	∿19	∿ 8
Round/oval	∿ 7	∿ 4	∿81	84
Pleomorphic	0	∿33	0	8
Staining (%)				
Eosinophilic	∿18	∿35	∿ 5	8.9
Orangeophilic	0	∿ 9	0	0
Cyanophilic	∿79	∿44	∿95	87.4
Chromatin pattern (%)				
Finely granular	almost 100	∿84	∿93	22.0
Coarsely granular	0	∿ 1	∿ 7	71.6
Opaque	0	∿15	0	6.4
Dirty smear	0	0	0	0
Macronucleoli	0	0	0	0

I. Reporting and Interpretation of Cytologic Findings

Papanicolaou introduced the classification into groups I–V for purposes of cytologic reporting. This classification is of historic interest, but in the light of present knowledge must be regarded as obsolete (*Soost* 1973). Nowadays, cytologic findings are interpreted by arranging the results into carefully defined groups based on the system of histologic reporting and the relevant recommendations of WHO regarding the classification of cytologic findings. The schedule illustrated in Table 5 was worked out in Munich in 1975 and is now widely used in German-speaking countries.

The first main group is subdivided into categories I and II. Smears in which all the cells are perfectly normal are placed in category I, while category II is intended for

Table 3. Criteria for the diagnosis of squamous carcinoma of the cervix uteri (adapted from *Koss* 1968; *Patten* 1973, 1976)

Criteria	Keratinizing squamous carcinoma	Large cell squamous carcinoma	Small cell squamous carcinoma
Cell area (μm^2)	275 ± 107	256 ± 69	169 ± 37
Nuclear area (μm^2)	77 ± 28	88 ± 30	65 ± 13
Relative nuclear area (%)	29 ± 6	34 ± 6	39 ± 6
Cell arrangement (%)			
Isolated	87	∿51	∿50
Aggregates	13	∿49	∿50
Cell configuration (%)			
Polygonal	Predominantly polygonal,	∿ 2	
Round/oval	> 15%	∿77	
Polymorphic	elongated cells	∿21	Predominantly polymorphic
Staining (%)			
Eosinophilic	Almost exclusively eosinophilic and orangeophilic	∿20	
Cyanophilic		∿ 55, the remainder amphophilic	Almost exclusively cyanophilic
Chromatin pattern (%)			
Finely granular	22	∿17	∿12
Coarsely granular	59	∿73	∿80
Opaque	19	∿10	∿ 8
Macronucleoli	Very uncommon	Occasional	∿5%
Dirty smear	Relatively uncommon	Frequent	Almost invariable

smears which contain inflammatory, regenerating, metaplastic, or degenerating cells. Smears showing signs of hyperkeratosis or parakeratosis also come into this category. If these changes are conspicuous, the cytologist may recommend that the smear should be repeated, but this decision will be influenced by the history and clinical findings.

Category III covers all smears with abnormalities in the squamous or glandular cells, in which for any reason a definite cytologic assessment cannot be arrived at. This difficulty is most frequently caused by severe inflammatory or degenerative changes, the individual cells being so poorly preserved that reliable cytologic classification is impossible. When a smear is classified under category III it is essential to carry out cytologic follow-up at short intervals, if necessary after giving appropriate treatment to clarify the picture. In some instances the cytologist may have to recommend biopsy and histologic examination.

Table 4. Criteria for the identification of endocervical glandular cells (adapted from *Reagan* and *Ng* 1973; *Schneider* and *Staemmler* 1976)

Criteria	Normal and endocervical cells	Highly differentiated	Poorly differentiated
Cell area (side view, μm^2)	188 ± 40	167–187	201–315
Nuclear area (μm^2)	54 ± 8	73– 85	97–165
Relative nuclear area (%)	31 ± 4	44– 46	50– 53
Cell arrangement	Isolated or in large groups	Isolated and in groups. Side-by-side arrangement is common in loose cell clusters	
Cell configuration	Side view: tall columnar cells in clusters; palisade arrangement. Seen from above: honeycomb pattern, isolated cells; basal nucleus; cilia or terminal bars often discernible	In well-differentiated carcinomas mainly columnar; with increasing dedifferentiation: rounded and oval cells with increasing numbers of tumor cell groups	
Cytoplasm	In cell clusters often well preserved and relatively well demarcated. In isolated cells the cytoplasm is usually ragged, or they may be reduced to bare nuclei, often in strands of mucus	Cells from a well-differentiated carcinoma usually have sharper outlines and a wider cytoplasmic zone than cells from an adenocarcinoma of the endometrium. Cells from undifferentiated carcinomas usually have ill-defined cytoplasmic margins. Fine diffuse vacuole formation or fine cytoplasmic granules	
Staining	Predominantly basophilic	Predominantly eosinophilic	
Nuclear structure	Round/oval, fine chromatin network	Round/oval. Up to 90% finely granular, sometimes chromatin bands or coarse chromatin scales. Hyperchromasia.	
Macronuclei	None	Usually several round nucleoli. Approx. 62% micronucleoli, approx. 38% macronucleoli; nuclear membrane nearly always sharply demarcated.	
Smear background	Clean	Dirty in up to 85%	

Table 5. Documentation of cytologic findings and further management required (Munich schedule)

Group	Cytologic findings	Further measures
I	Normal cells	
II	Inflammatory, regenerative, metaplastic or degenerative changes; hyperkeratosis and parakeratosis cells	Repeat smear if necessary
III	Severe inflammatory or degenerative changes and/or poorly preserved cells; dysplasia, carcinoma in situ or invasive carcinoma cannot be excluded; atypical gland cells and stroma cells from the endometrium after the menopause	Cytologic follow-up at short intervals, if necessary after hormone treatment; possibly biopsy as well
III D	Cells from dysplasia of mild or moderate grade	Cytologic follow-up in 3 months
IV a	Cells from severe dysplasia or carcinoma in situ	
IV b	Cells from severe dysplasia or carcinoma in situ; invasive carcinoma cannot be excluded with certainty	Biopsy required
V	Cells from an invasive carcinoma of the cervix or other malignant neoplasm	
0	Technically unsatisfactory (e.g., insufficient material, inadequate fixation)	Repeat smear without delay

Category III D contains all forms of dysplasia of mild or moderate degree. As explained earlier, it is for various reasons impossible to offer a definite opinion regarding the prognostic significance of such changes. Statistical follow-up studies have shown that spontaneous regression can be expected in some 60% of such cases. The cytologist should therefore recommend repeat smears at intervals of 3 months. Only when the change progresses or remains unchanged for more than 1 year should it be removed by conization.

The last main group is subdivided into categories IV a, IV b, and V. It comprises all those cytologic findings which demand immediate histologic clarification. Severe dysplasias and carcinoma in situ are placed in group IV a. Group IV b comprises those smears which must be assessed as showing severe dysplasia or carcinoma in situ, but where an invasive carcinoma cannot be excluded beyond doubt. "Microcarcinoma" also comes under this heading.

Smears which contain cells of invasive carcinoma are classified under group V. The cytologic diagnosis of tumor type should be undertaken during the final evaluation of the smear as a whole. The cytologic criteria available for this purpose have already been discussed in detail.

The heading "technically unsatisfactory" is used for smears which do not contain any representative cell material or which, owing to technical shortcomings, are unsuitable for cytologic assessment.

From what has been said it will be evident that cytology constitutes a screening method which can be used to detect silent neoplasms and precancerous changes, so that appropriate information can be given to the clinician. A presumptive cytologic diagnosis must, as a rule, be confirmed by histologic examination. The gynecologist will base his definitive therapeutic plan on the sum total of information provided by all available diagnostic techniques. The trustworthiness of cytologic examination is influenced by the site of the lesion and is almost totally dependent on good technique in the collection of smears and on the efficiency of the cytologic laboratory. Given satisfactory smears, an experienced cytologist can achieve a "pickup rate" of over 90% in cases of dysplasia, carcinoma in situ, and squamous cell carcinoma (*Patten* 1969; *Wied* et al. 1976).

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Histologic Verification of Cervical Cancer

J.-H. HOLZNER

A. Introduction

The development of cytology and colposcopy during recent decades has led to a high degree of diagnostic accuracy of these methods in the detection of early stages of cervical cancer. Although it is possible to detect even microinvasion by cytology alone, as has been shown by *Ng* et al. (1972), a histologic diagnosis performed on tissue sections is still required for a definitive morphologic confirmation of the lesion. This is necessary for several reasons: First, the cytologic differentiation between preinvasive and invasive cancer is still burdened with a certain percentage of diagnostic uncertainty which varies according to the experience of the cytologist and the quality of the smear. Second, an optimal treatment of a neoplastic lesion must be based on a clear morphologic diagnosis, including exact staging and grading. Furthermore, other important diagnostic questions such as the determination of the surface extension of the lesion and the invasion of lymphatics, which cannot be answered by cytologic investigation, may be cleared up histologically. Small lesions can be removed completely by diagnostic cone biopsy, so that the diagnostic procedure may become an important part of therapy.

The histologic evaluation of bioptical material to provide a sufficient, accurate, and definitive diagnosis requires representative and well-preserved tissue. This can be gained by various surgical methods. Many arguments have been used for and against some of these methods in the last few years, and technical problems as well as financial questions have been included in these discussions. As there is still no complete agreement on the optimal diagnostic procedure, the different methods for the histologic verification of a positive smear will be discussed critically.

The histologic confirmation of cervical neoplasia can be based on several bioptical techniques:

1. The single colposcope-oriented punch biopsy of the suspicious area.
2. Multiple punch biopsies of the external os, when there is no visible lesion.
3. The endocervical curetting when the cytologic smear suggests an endocervical neoplasm.
4. The conization biopsy with different variations, such as shallow conization for ectocervical and deep conization for endocervical lesions.
5. The combination of two or more of the methods mentioned above.

B. Single Punch Biopsy

The single punch biopsy for histologic verification of cervical neoplasia may be of sufficient diagnostic accuracy when certain conditions exist. Most important of all, the suspicious area should be visible either by colposcope or by colpomicroscope, and the location of the lesion should make it possible for the biopsy to be taken under colposcopic or colpomicroscopic control. In all other cases – especially when no visible lesion exists in spite of highly suspicious cytologic finding – other diagnostic procedures should be chosen, such as conization biopsy, multiple blind biopsies, or endocervical curetting, the latter when the cytologic findings are highly suggestive of endocervical neoplasia.

A single punch biopsy from the portio of the uterus means only slight or no inconvenience for the patient. The biopsy may be taken in an out-patient department, the patient does not have to stay at the hospital, and this type of surgical procedure has practically no complications.

The result of the histologic evaluation may be obtained within 10–15 min when using the frozen section technique, or within 12–24 h when using the usual paraffin-embedding technique. Therefore, further diagnostic procedures, if necessary, or treatment can start without delay.

The biopsy should be taken under exact colposcopic or colpomicroscopic control. The tissue should be removed very carefully, avoiding mechanical destruction and squashing. It should then be placed on a piece of paper towel, the mucosal surface facing upward. The specimen should then immediately be placed upside-down in a suitable fixative for optimal nuclear fixation (for instance, Bouin's solution), with the mucosal surface of the specimen facing the bottom of the container. In this way, the tissue will be fixed undistorted and may be embedded in paraffin without losing the possibility of orientation. This is very important, as for optimal evaluation the sectioning should be performed exactly perpendicular to the mucosal surface. For optimal histologic evaluation serial sections or gradual serial sections, which means taking each tenth or twentieth section for example, should be cut. For each section stained with hematoxylin and eosin one or more parallel sections should be kept for special staining if this turns out to be necessary: for instance, mucous staining for mucoepidermoid carcinoma, or reticulin stain for nonepithelial or mixed neoplasms.

If the removing and processing of the biopsy material has been done adequately, the single punch biopsy will lead to a final diagnosis in all cases of invasive cancer. In cases of preinvasive lesions (cervical intraepithelial neoplasia), further diagnostic pro-

cedures are necessary if the lesion has not been entirely removed by the biopsy. The diagnosis "cervical intraepithelial neoplasia" ("carcinoma in situ," "intraepithelial dysplasia") can only be made when it can be proved by serial sections that the entire lesion has been completely removed by the punch biopsy, and when it is separated by normal epithelium from the margins of the tissue sample taken bioptically. It is clear that this decision will be possible only if the tissue has been processed in the manner mentioned above, and that there will always be a certain number of cases in which further diagnostic procedures will be necessary. In our own material (*Wunderlich* and *Holzner* 1971), this was the case in 45.6% of 392 cervical punch biopsies, and in 35.5% of 307 biopsies, when the biopsy was taken because of clinical and cytological high suspicion of invasive cancer. In these cases the method of choice will be diagnostic conization, but it must be taken into consideration that the evaluation of the cone biobiopsy may be difficult due to the inflammatory reaction present on the site of the previous punch biopsy.

Therefore, the main indication for a single directed punch biopsy for verification of cervical neoplasia will be a positive PAP smear, indicating a suspected invasive cancer, and a lesion visible by colposcopy and removable by one single biopsy under colposcopic control. The evaluation should be performed in a pathology laboratory with facilities for optimal processing and working up of the tissue sample.

C. Multiple Punch Biopsies of the External Os

In cases with a positive PAP smear, suggesting an ectocervical or junctional (squamocolumnar junction) neoplasia, but without any colposcopically visible abnormality, multiple blind biopsies can be taken as an alternative method to the conization biopsy. The advantages of this procedure lie exclusively on the side of the patient, as the biopsies can be taken on out patients and no admission to the hospital is necessary; the histologic diagnosis will be available within 24 h. But there are a number of disadvantages associated with using this method from the diagnostic point of view. In most cases the exact determination of the extension of the lesion will not be possible and in most instances it will also be impossible to determine if a lesion has been removed completely or not. Therefore, a follow-up conization biopsy must be performed in most cases, the evaluation of which will be extremely unreliable due to the mechanical destruction of the mucosal surface at the sites of the biopsies taken previously.

Therefore, in agreement with most authors, we do not recommend this procedure and prefer the diagnostic conization, which gives much more reliable results, though at a higher cost and with greater risk of complications.

If the multiple-biopsy technique is chosen, the processing of the tissue samples must be performed exactly in the same manner as was outlined for the single-biopsy technique. Each specimen must be labeled and its topographical site on the portio marked on a drawing.

D. Endocervical Curettage

An endocervical curettage is usually performed in conjunction with one of the other diagnostic procedures. As a single method it is used only in rare instances. An endocervical scraping may lead to a satisfactory final diagnosis if the positive cytologic smear indicates an endocervical type of neoplasm, e.g., endocervical adenocarcinoma, and is highly suspicious of an invasive lesion. As a combined method the endocervical curettage makes it possible to determine whether the cervical canal harbors invasive or non-invasive cancer.

The specimen obtained by endocervical scraping usually consists not only of endocervical tissue fragments, but also of mucous and blood. Because it is necessary to investigate even the tiniest tissue fragment, and in order not to lose a single one during laboratory processing, the whole sample, including blood and mucous, should be collected carefully by the surgeon and placed on a sheet of paper towel. The fixation should be performed in a fixative with optimal preserving properties for the nuclear structure (e.g., Bouin's solution). The embedding of the material should be done without loss of any piece of tissue, blood, or mucous and in a way that makes at least some topographical orientation possible for the histologic investigator. A gradual serial sectioning should be performed, and some unstained sections should be kept for special staining methods.

In most instances it turned out to be advantageous to combine the endocervical curettage with an endometrial curettage. A possible progression of the lesion to the endometrium may be excluded in this way. Furthermore, in positive cytology suggestive of adenocarcinoma and with negative histologic findings on the portio and endocervix, a histologic investigation of the corporal endometrium must be performed in any case.

The endocervical curettage will lead to a final diagnosis only in cases of invasive cancer. When preinvasive lesions are found, further diagnostic methods must be performed in all cases. Due to the technique of scraping, it is not possible to get one single piece of tissue in which a topographic orientation and determination of the extension of an abnormality would be possible. There are always more or less numerous pieces of tissue obtained, some of them very small, which cannot be located retrospectively with regard to the different parts of the cervical canal.

Therefore, the main indications for performing an endocervical curettage as a single diagnostic procedure are cases with positive PAP findings highly suggestive of an endocervical (adenomatous) invasive neoplasia and without any lesion on the portio visible by colposcopy. Combined with other diagnostic methods, the endocervical scraping may reveal valuable additional information, e.g., about the endocervical extension of an invasive or preinvasive lesion on the ectocervical surface of the uterine portion.

E. Diagnostic Conization Biopsy

The conization biopsy specimen consists of a conical structure of tissue of varying size, containing the external os and the endocervical canal, or a part of it, in the center of the cone. The base of the sample represents the ectocervical mucosa surrounding the external os. The innermost end of the part of the cervical canal removed by the biopsy is represented by the apex of the cone. The outer surface of the specimen marks the cutting surface. In cases of a predominantly ectocervical location of the neoplastic progression, a shallow cone may be performed, but in cases of cancerous lesions extending into the cervical canal a deep cone must be taken. The technique of removing and processing the tissue sample is the same in both instances.

The specimen should preferably be taken by the cold-knife technique in order to preserve the cutting surface for an histologic investigation. This is of great importance for further diagnostic or therapeutic management if the lesion extends close to the margin of the tissue sample removed by biopsy. The operation should be performed with great care. It is necessary to avoid any touching of the mucosal surface of the ectocervix with sharp instruments. The portio should be hooked outside the cutting line, and the cone itself should not be grasped on the mucosal surface, but on the outer cutting surface exclusively (*Burghardt* 1972). If it proves necessary to combine a conization biopsy with an endometrial and/or endocervical curettage, the dilatation of the canal and the curetting should always be performed after taking the cone biopsy. Staining of the uterine portio with Lugol's solution in order to determine the extension of an abnormal epithelium prior to the biopsy, or infiltration of the tissue with vasoconstrictive drugs in order to reduce bleeding during the operation (*Burghardt* 1963a, b; *Burghardt* and *Albegger* 1969; *Scott* et al. 1960) has no influence on the quality of the histologic processing.

The specimen should be received fresh by the processing laboratory. In order to avoid any mechanical destruction of the epithelial surface, it should not be opened by the clinician. If transportation to the laboratory does not occur immediately, the specimen must be placed in a suitable fixation solution (preferably Bouin's solution) immediately after being removed from the uterus and before managing the wound. The volume of the solution should be at least five times that of the specimen. When an opening of the external os cannot be avoided during the operation, e.g., due to an extremely dilated cervical canal, the cone should be reconstructed and sewed up with one or two sutures before being placed in the fixative solution (*Burghardt* 1972).

The further processing of the conization specimen can be performed in several different ways (*Artner* et al. 1972; *Burghardt* 1972). Before going into detail the most important questions for the diagostic evaluation of the conization have to be outlined. These are:

a) Type of epithelial abnormality (intraepithelial or invasive lesion, histologic type of neoplasia, grade of anaplasia).
b) Location and extension of the lesion.
c) Presence and type of stromal reaction, involvement of blood vessels and/or lymphatics.
d) Evaluation of the cutting surface in order to determined if a lesion has been removed completely by the biopsy or not.

Thus, the main aims in processing the material are to maintain the possibility of orientation within the sections and the possibility of a three-dimensional reconstruction after histologic evaluation of the sections, and to preserve the cutting surface for exact investigation. The four different methods used most widely are described below:

1) Excellent results can be obtained by dividing the cone into two equal halves by cutting it at a median level (*Artner* et al. 1972; *Burghardt* 1963a; *Fettig* and *Hillemanns* 1962; *Kern* 1964; *v. Matuschka* 1972). The two halves are then each embedded as a whole. If the fixation of the tissue samples seems to be insufficient due to the size, a postfixation of the sections with 10% formalin is possible. If the diameter of the cone is very large, each half may be divided into two pieces parallel to the first cutting. The two halves are marked "A" and "B," or, in the case of further division of the cone, "A1," "A2," "B1," and "B2" (Fig. 1a).

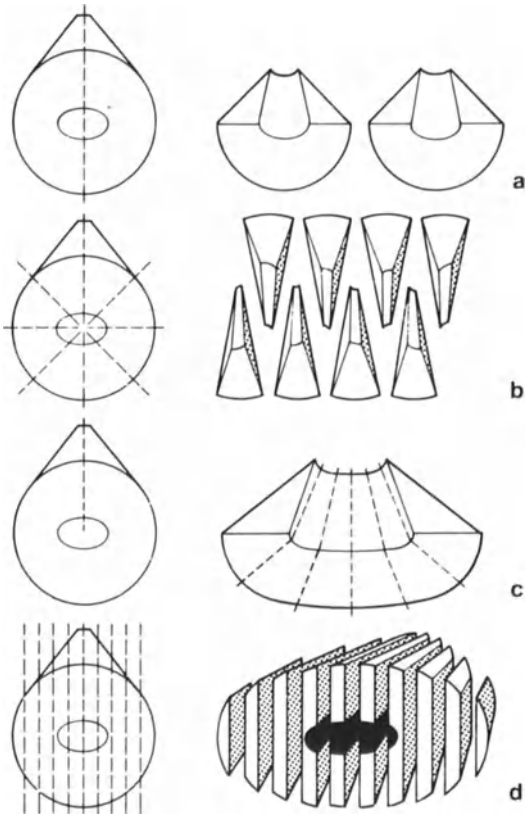

Fig. 1a–d. The different techniques for the dissection of the conization specimen (see text)

The sectioning of the embedded halves has to be performed parallel to the median cutting surface. Thus, each section represents one level through the entire cone containing the whole endocervical canal, and the anterior and posterior margin of the specimen. Therefore, the exact location and determination of the extension of a lesion is possible without difficulty. The margin of the specimen can be evaluated in

each single section. The knife of the microtome should be directed to the epithelial surface of the cone, otherwise parts of the ectocervical mucosa may be torn off during sectioning, making a critical evaluation impossible. Usually every 10th to 30th section is placed on a slide for H & E staining, the others being discarded. Two or three sections may be placed on one slide. It may be of advantage to keep one or two parallel sections to each H & E section unstained for special staining later, if this turns out to be necessary (see processing of "single punch biopsy"). The sections mounted on slides are numbered, beginning from the center of the cone ($A_{1, 2, 3 \ldots}$, $B_{1, 2, 3 \ldots}$).

In a first step the two halves of the cone are sectioned until the cervical canal disappears from the sections. In those cases in which the lesion is limited to the external os, further processing of the two halves may not be necessary. But if the lesion is still present in the last section, which means that it extends onto the ectocervical surface, a further sectioning of the half involved has to be performed. In lesions extending to, or close to, the ectocervical margin of the specimen the whole specimen must be worked up.

As the thickness of the sections (usually 5–7 μm) and the number of discarded sections (9–29) are known, a three-dimensional reconstruction of a lesion may be possible; its volume, important for prognositic evaluation can then be determined.

2) Some authors (*Christopherson* and *Parker* 1961; *Fidler* and *Boyes* 1959; *Moore* et al. 1961; *Scott* and *Ballard* 1962) recommend a dissection of the cone by radial sections (Fig. 1b) directed to the center of the cervical canal, thus obtaining eight to ten radial sectors of the specimen. The dissection must be performed after fixation. Each sector is then embedded separately and marked.

The sectioning of the blocks starts parallel to one of the cut surfaces. Thus the sections are of triangular shape, outlined by the ectocervical mucosal surface, the endocervical canal, and the outer cutting surface of the cone. But as the thickness of each block increases from the cervical canal to the periphery, the later sections of each block will represent peripheral parts of the cone only, no longer extending to the cervical canal. Therefore, a three-dimensional reconstruction of a lesion will be more difficult since the level of the sections is disadvantageous in this respect. Furthermore, each block covers only one sector of the whole cone; therefore, the overall number of sections will be much higher than in method 1, where the cone has to be worked up completely.

3) A variation of the technique described in method 2 has been used by *Beyer* (1964), *Braitenberg* and *Schüller* (1963), *Ferenczy* (1977) and *Gray* (1964) (Fig. 1c). The fresh unfixed specimen is opened in the middle of either the anterior or the posterior lip, pinned on a cork board, and so fixed. After fixation, 2–5 mm thick sectors are cut perpendicular to the surface and the cervical canal, and then embedded separately into paraffin. The sectioning of the blocks is performed in the same way as in method 2, leading to the same disadvantages, but with a somewhat better topographical survey for a three-dimensional reconstruction.

4) A variation of method 1, which may in some cases reduce the number of sections necessary, is the division of the fixed cone in several or more parallel blocks by cutting it in a sagittal direction, each block having a thickness of 3–5 mm (*Brangle* et al. 1963; *Böhm* 1976; *Fluhmann* 1961; *Kern* 1964; *Ober* and *Bötzelen* 1959; *Ober* 1969) (Fig. 1d).

Each block is embedded into paraffin and, as a first step, a few sections are obtained from each block and labeled with the number of the block and the section. Thus, the whole specimen may be quickly examined using a relatively low number of sections. The further sectioning of the embedded blocks may be limited to those blocks in which epithelial abnormalities have been found by reviewing the first sections. Thus, with this procedure the overall number of sections may be significantly reduced in comparison with methods 1, 2, and 3.

If a deep cone has been performed, a variation of the dissection of the cone specimen may be used and is applicable to all methods described. First, the apical part of the cone is topped. In methods 1, 2, and 4 this can be done after fixation, but in method 3 it must be done before opening the cone and therefore before fixation. The apical part, which is embedded separately, is dissected perpendicular to the cervical canal. Thus, the latter is located in the center of each section. It seems advantageous to start sectioning at the base of the block and to end up at the apex. The basal part of the cone may be worked up in one of the methods described. This variation has been used by *Dubrauszky* (1962).

F. Combined Methods

A combination of several procedures is recommended by several authors (*Burghardt* 1972; *Ferenczy* 1977) in order to reduce the number of conization biopsies because of cost and the higher risk of complications. As a first step they recommend a directed punch biopsy when visible lesions are present or an endocervical scraping when the colposcopic findings are normal; both may be followed by diagnostic conization if necessary.

Although there is no questioning the high diagnostic accuracy of the conization and its therapeutic properties in cases when the lesion has been completely removed by conization (*Anderson* and *Linton* 1967; *Braitenberg* and *Schüller* 1962; *Chao* et al. 1969; *Ferenczy* 1977; *Govan* et al. 1969; *Pantucek* and *Holzner* 1975; *Sabatelle* et al. 1969; *Stucin* 1966; *Wunderlich* and *Holzner* 1971), there is incomplete agreement as to the indication of a conization biopsy as a first and only procedure for the histologic verification of an epithelial abnormality of the cervix. The advantages and disadvantages of punch biopsy and conization have been compared by several investigators (*Hulka* 1970; *Pantucek* and *Holzner* 1975; *Sabatelle* et al. 1969; *Selim* et al. 1973), as well as the value of cone and punch biopsy (*Burghardt* 1963a; *Dubrauszky* and *Mbiye Kamuma* 1970; *Krupitz* 1974; *Shulman* 1963; *Silbar* and *Woodruff* 1966; *Singleton* and *Rutledge* 1968; *Thompson* et al. 1972; *Wunderlich* and *Holzner* 1971).

The high diagnostic accuracy of the conization biopsy makes further diagnostic procedures unnecessary in almost 100% of cases. A diagnostic conization may answer the following diagnostic questions:

1. The extension of the neoplastic lesion can be determined on the epithelial surface as well as within the cervical wall. Using a three-dimensional reconstruction, calculation of the volume of the neoplastic tissue is possible; this has proved of great value in the prognostic judgment of the disease.

2. The type and degree of invasion, including the involvement of lymphatics and blood vessels, can be clearly determined, as can the type and intensity of a stromal reaction resembling immunologic defence.

3. Due to the amount of tissue available for investigation in a cone specimen, the detection of more than one foci of invasion will be possible, which may be overlooked in single punch biopsies.

4. Conization biopsy makes available enough tissue for a special and more detailed investigation, as well as for scientific purposes.

5. In cases where the entire lesion is seen within the specimen, the conization biopsy may not only be of diagnostic value, but it may be the optimal therapeutic procedure as well.

Depending on the amount of normal tissue lying between the carcinomatous lesion and the margin of the cone, the following guidelines can be used to determine the radicality of the excision:

1. If the distance between the abnormal epithelium and the apex of the cone or the outer cutting surface is more than 10 mm, the lesion can be regarded as "entirely removed and far from the margin" (Fig. 2a).

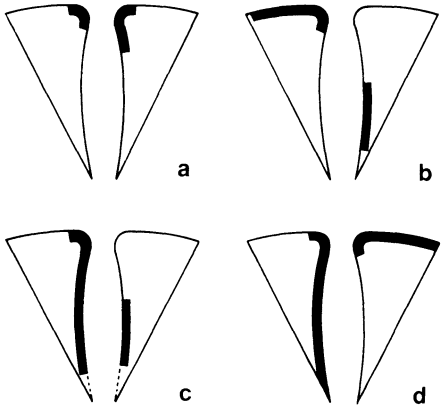

Fig. 2a–d. Evaluation of the radicality of the excision of a neoplastic lesion on a cone. **a** Lesion entirely removed, far from the margin. **b** Lesion entirely removed *(right side)*, just entirely removed *(left side)*. **c** Lesion not certainly removed (epithelial defect between lesion and apex). **d** Lesion not completely removed

2. If the distance between margin and lesion is between 2 and 10 mm, the lesion can be regarded as "entirely removed." When there is only a small area of normal epithelium separating the lesion from the margin and measuring less than 2 mm, the lesion can be classified as "just completely removed" (Fig. 2b).

3. When the neoplastic lesion does not reach the margin of the specimen, but when there is no normal epithelium preserved due to an epithelial defect or to an artefact, the lesion is "not removed with certainty" (Fig. 2c).

4. If the neoplastic tissue extends to the margin of the section, so that the cutting surface goes through the neoplastic area, the lesion is "not completely removed" (Fig. 2d).

This classification used in our laboratory is appreciated by the clinicians and gives them valuable information about the further therapeutic management of the case.

The degree of invasion is classified in the following way:

1. No stromal invasion (carcinoma in situ, dysplasia, intraepithelial neoplasia).
2. Beginning stromal invasion (borderline case with some diagnostic uncertainty).
3. Microinvasion: an undoubted stromal invasion, but usually less than 3 mm.
4. Deep stromal invasion of more than 3–5 mm.

In cases of stromal invasion, the type and degree of involvement of lymphatics and/or blood vessels should be reported separately.

When a recommendation of the best diagnostic procedure for the histologic verification of cervical neoplasia is to be given, one has to consider the most important features for the clinician, which are the following:

1. Invasive carcinoma must be ruled out.
2. If the lesion turns out to be non-invasive, its distribution has to be determined.
3. The lesion should be removed in the easiest, most reliable, and least costly way possible, and, if appropriate, the patient's reproductive functions should be preserved (*Ferenczy* 1977).

Therefore we recommend the following procedure:

In cases of advanced cancer, in which invasion is unquestionably present, a directed single punch biopsy will provide sufficient diagnostic accuracy for the verification of the disease.

If the neoplastic lesion has been detected by cytologic smear, further diagnostic management depends on the quality of the cytology and histology units available:

1. When there are *optimal conditions,* which means a highly qualified cytologic unit with a high diagnostic accuracy record regarding non-invasion, microinvasion, and invasion and a highly qualified histologic unit able to process the samples in the optimal manner:

Positive PAP smear suggesting an invasive lesion:

a) Colposcopically visible: directed punch biopsy.
   (i) Stromal invasion proved by histology: no further diagnostic procedure.
   (ii) No stromal invasion: diagnostic conization.
b) No visible lesion by colposcopy: diagnostic conization (with endocervical curettage).

Positive PAP smear suggesting microinvasion:

a) Lesion visible by colposcopy: directed punch biopsy or diagnostic conization (the latter preferred in our unit).
b) No visible lesion: diagnostic conization.

Positive PAP smear suggesting intraepithelial neoplasia:

a) Lesion visible by colposcopy: diagnostic conization. (Some authors recommend punch biopsy in these cases. But if the lesion proves not to have been entirely removed by the biopsy, diagnostic conization must follow).
b) No visible lesion: diagnostic conization (with endocervical curettage).

2. When the conditions regarding accuracy of cytology are not optimal, which means a low degree of diagnostic accuracy in a cytologic differential diagnosis of the degree of invasion:

Positive PAP smear with an abnormal colposcopic finding: Directed punch biopsy (followed by conization, when the lesion turns out to be non-invasive and/or not entirely within the biopsy specimen) or diagnostic conization as prime procedure.

Positive PAP smear with normal or unsatisfactory colposcopic findings: diagnostic conization (with endocervical curettage).

Endocervical curettage is an optional procedure in addition to diagnostic conization in cases suggestive of an extension of the cancerous lesion into the upper parts of the cervical canal, or when a shallow cone biopsy has to be performed for other reasons.

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Precursors of Cervical Cancer

Etiology and Epidemiology of Cervical Cancer

I.D. ROTKIN

The surfeit of recent cervical cancer epidemiologic reviews is indicative more of academic labor than of contribution to the mainstream of developing risk and control information, or of derived insights. Some of these efforts have persisted in attempts to establish favored but hardly favorable risk hypotheses, viral and otherwise, rather than to deal with issues projected into the present by overwhelming evidence covering many consistent studies.

After the surge of research beginning in the early 1950s and extending through the 1960s, it seemed that long-sought clarifications regarding accumulated demographic and risk information had finally been reached. There was still no satisfactory explanation for the remarkably low incidence of cervical cancer among Jewish women everywhere in the world, the long-held theory of noncircumcision in sexual mates having been abandoned (*Rotkin* 1973), but centrality had been established earlier for the wide diversity of speculations regarding factors which could increase the risk of cervical cancer. It was announced at that time that the two key variables to which most other claimed events, attributes, and exposures could be related were: coital beginnings during adolescence by women at risk, and sexual encounters with multiple partners (*Rotkin* 1962). Identification of these two biologic variables resolved or set aside such old speculations as early, broken, and multiple marriages; multiple gravidity and parity; derivation from impoverished social classes; excessive morbidity and mortality rates in specific ethnic populations; lacerations resulting from coitus or parturition; and male preputial smegma as a carcinogen against which labial and vaginal tissues were somehow protected, yet the remaining residue of which appeared to initiate carcinogenesis specifically at the squamocolumnar juncture of the endocervix, a position which the many years of preoccupation with prepuces had failed to demonstrate. There was, further, the power of the new sexual findings (*Rotkin* 1962, 1967a), now among the most secure of all chronic disease epidemiologic relationships. To date, no population in the world has been found in which early coitus is widespread and where incidence of cervical cancer is not high.

Most important is that a rationale was evolved to explain the heavy burden of evidence (*Rotkin* 1967a, 1972). In essence, this assumed a high degree of cellular activity during adolescence with maximal opportunity for oncogenic transformation of selected cervical cells; and, further, that since no demonstrated virgin had ever been diagnosed with a squamous cell cervical carcinoma, introduction of an oncogenic agent of some kind was required to initiate the process.

That a horizontally transmitted substance or organism might lead to carcinoma was not a new concept. During his speculations on the relatedness of phimosis and penile

cancer, *Handley* (1936) had mused that a "marital" bacterial infection might also cause cervical cancer. He espoused prophylactic male circumcision, as have so many others since then, following attempts to identify male smegma as a sexually transmitted carcinogen. Such attempts inaugurated a substantial literature based on laboratory efforts to induce cervical carcinomas in mice, but without resolution. It was not, however, until later studies (*Wynder* 1954; *Rotkin* 1954; *Terris* and *Oalmann* 1960) that age at first coitus was included as a case-control variable, to be followed by identification of this specific variable, and also multiple sexual partners, as those with a direct and central bearing upon increased risk (*Rotkin* 1962).

One outcome of these reports was a growing literature which has branched off into a search for venereally transmissible oncogenic agents, the theory of contribution of some such agent by the male having found widespread acceptance, and the identified variables having since been repeatedly demonstrated in many studies. Earlier reports had already proposed commonplace venereal disease bacilli to be associated with cervical cancer (*Levin* et al. 1942; *Rǿjel* 1953). Several new agents were proposed as candidates, including spermatozoa as the oncogenic component of the ejaculate (*Reid* 1965), and also herpes simplex virus type 2 (*Rawls* et al. 1968), both still unresolved with regard to risk. It might be said with some justification that the epidemiology of cervical cancer had been solidly established and that further research had been transferred into the laboratory.

A convincing response to a number of questions, some of which may touch on a general understanding of carcinogenesis, remains to be found. One of the newer developments is the proposal that the generally accepted view requiring direct alteration of chromosomal DNA for oncogenic transformation of the normal cell may be reexamined in favor of other alternatives (*Singer* et al. 1976). Some of us have long felt uneasy over the stubbornly held assumption that rearrangement or impairment of one or several specific chromosomal nucleotides is required for onset of carcinogenesis. The further suggestion by the same group that certain proteins derived from spermatazoa (a histone and a protamine) constitute oncogenic influences upon the histogenesis of cervical cancer is another matter which demands hard evidence in face of the realization that such a situation could give rise to so much cervical cancer that the human species would be endangered. But the possible abandonment of cherished beliefs in favor of new ideas is an important trend.

The other direction of inquiry has been an unexpected emphasis upon medical and social problems arising from the background of epidemiologic and biologic research, in particular from demands for justification of screening procedures to detect early cervical carcinomas; and most urgently, proposals for the modification of adolescent female sexual behavior as a measure of prevention which would further reduce mortality from cervical cancer. This chapter will be concerned only with a review of demographic, etiologic, and epidemiologic currents of investigation leading to outcomes upon which rest some of today's most pressing issues related to risk, rates, detection, and prevention of cervical cancer. The issues will be discussed in a separate publication.

Beginnings. Credit for preparation of the soil out of which grew the most comprehensive epidemiologic appraisal of any cancer, with seeds scattered throughout the world, goes to *Domenico Antonio Rigoni-Stern* (1842), the still inadequately heralded Italian physician at the University of Padua whose studies in Verona initiated demographic cancer comparisons, with emphasis upon mortality rates not only among women in the general population, but also in a specific segment characterized by celibacy, i.e., Catholic nuns. There was precedence for his selection of this target group and for his methodology. Earlier, *Ramazzini* (1700) had associated the celibacy of nuns with higher frequencies of breast cancer, whereas *Tanchou* (1844), a contemporary of *Rigoni-Stern,* had collected comparison cancer mortality data for Parisian men and women. The full history of the beginnings of epidemiologic cancer research can be found in *Shimkin*'s monumental volume (1977). Latent appreciation of *Rigoni-Stern* as the giant in medical history who conceptualized and synthesized cancer demography, statistics, and epidemiology is attributed to *Clemmesen* (1951) and is detailed in a number of publications (*Mustacchi* 1961; *Rotkin* 1973).

Since differentiation between carcinomas of the cervix and corpus was not made until the twentieth century, early investigators classified all such cancers as uterine. *Rigoni-Stern* concluded that uterine cancers are excessive in married women, quite unusual in unmarried women, and virtually absent in the orders of nuns whose death records were studied. He also observed an inverse relationship between frequencies of uterine and breast cancer, with excesses of uterine cancers and deficits of breast cancers in married women, against the reverse in unmarried women. When rediscovered, these results, detailed and tabulated in a manner that would be acceptable today, initiated new investigations covering populations of nuns on the premise that women of these orders had maintained celibacy throughout their lives.[1] The subject of celibacy in relation to cervical cancer risk will be developed later in this chapter.

Since then, failure of a squamous cell carcinoma of the cervix to be reported in confirmed virgins (with one exception) has led first, to an emphasis upon marriage and other sociocultural variables as an explanation of increased risk, perhaps as a puritanical avoidance of sexuality as the key issue which early findings on celibacy would indicate, and also to a range of biologic hypotheses, the most persistent of which was derived from the relative worldwide immunity of Jewish women to invasive cervical cancer. Epidemiologic research was obsessed for several decades with the reasoning that since all Jewish men are circumcised and few Jewish women are diagnosed with this carcinoma, noncircumcision was therefore the direct cause, an example of contrived logic which completely overlooked the failure of many studies to demonstrate such a relationship (*Rotkin* 1973). Publications were concerned with such minimally urgent issues as the relative lengths of natural and surgical prepuces and the reliability of circumcision data obtained from wives, husbands, and physicians, none of which appeared to classify prepuces convincingly.

The single report of cervical cancer in a virgin (*Mogaji* 1973), apparently verified by the presence of an imperforate hymen, was classified as a true squamous cell carcinoma. That no other such case has been validited may result from small numbers of

1 My own studies of 146 nuns in Chicago (unpublished) have revealed that 8% were not virgins, most of these having experienced coitus before entering the orders.

women who have remained virginal into later years, a general failure to report existing cases, the possibility that sexual penetration of the labia might have taken place without perforation of the hymen, or the highly unusual noncoital introduction of a strongly carcinogenic event which by itself could transform cells at risk.

A large step forward was taken in the report by *Lombard* and *Potter* (1950), in which a number of simultaneously studied variables were described, but with emphasis upon early marriage as the discriminating event increasing risk, and which preceded the current focus on sexuality. It should be noted, however, that *Clemmesen* (1951) had speculated earlier on the centrality of sexuality. Each of these various directions of inquiry will be considered in the section on epidemiology.

It is not the purpose of this chapter to present historical minutiae which have appeared so many times in the literature. Reference is made to selected reviews, some of which are positioned with regard to preferred viewpoints (*Reid* 1965; *Coppleson* 1969; *Heller* 1970; *Rotkin* 1973; *Canadian task force on cervical cancer screening programs* 1976; *Harington* 1977). Special reference is also made to *Auster*'s (1965) assessment of the background upon which the earlier preoccupation with noncircumcision rested as the endorsed cause of cervical cancer.

Worldwide Distribution: General and Special Rates. The geographic extent of cervical cancer can only be surmised as approximations to actual but unknown rates. Most data are from *World Health Organization* publications which summarize reports from participating populations, usually countries. Probably the most accurate morbidity and mortality rates are furnished by developed countries, but the incidence of cervical cancer is highest in developing populations, including those segments, such as nonwhites in the United States, now emerging. Diagnosis, medical reporting, and death records for these populations undoubtedly do not compare favorably with those of the established matrix populations, and rates generally must be considered as understated. Conversely, it is possible that those rates published in past decades are exaggerated, perhaps because information covered only selected groups seeking treatment.

The highest known incidence of cervical cancer is still found in Colombia, South America, formerly reported at about 110 per 100 000 population of all ages, and now listed in WHO rates for 1975 at 63 per 100 000 women. Developing Latin American countries, all report high morbidity and mortality from cervical cancer. Reasons are not difficult to find: the profile of the woman at highest risk of cervical cancer describes her origin in the lower economic classes, with the concomitant early onset of sexuality and many coital partners, life patterns characteristic of large proportions of populations in countries characterized by crowding and deprivation (*Rotkin* 1972). Typical is the *barriada,* an accumulation of minimal dwellings spread throughout urban areas, such as in Lima, where native inhabitants of the Andes have been migrating to the city in search of sustenance. Within these distributions of frustation, poverty, and illiteracy, preadolescent girls are often coaxed into coitus. Cancer of the uterine cervix is the most prevalent neoplasm among the female Peruvian population; this is true also for adjoining countries where conditions are similar. We will return to rates in these Latin American countries.

Information from a number of populations in past years supports the generalizaton that no geographic area has been studied which is characterized by poverty, high levels

of illiteracy, short life spans, and early sexual activity where rates of cervical cancer are not excessive. However, it seems true that certain European countries with homogeneous populations also have high rates, possibly as a consequence of abandoned sexual restraints. If there is one remarkable exception to these trends, it is the still unexplained extremely low rates of cervical cancer among Jewish women everywhere in the world, a subject to be discussed later in this chapter in the section on risk variables. Women of certain other populations also seem to be at relatively low risk; at least, they are so regarded in the absence of secure data: Irish and Italian immigrants, Seventh-Day Adventists, Amish, high sociocultural groups, and those in rural areas (*Martin* 1967). The long-held belief that Moslem women are seldom diagnosed with this cancer has been discounted by results of screening programs conducted around New Delhi, India (*Wahi* et al. 1969), during which 1 of every 100 Moslem women was found to have an invasive carcinoma. *Wahi* also diagnosed 1 in every 50 Hindu women with a cervical cancer, an extremely high rate which appears to be characteristic of much of India.

New studies report extremely low rates in Malaysian Orang Asli aborigines (*Sumithran* 1976), in the Bendel State of Nigeria (*Emovon* 1977), and among Mormon women in Utah (*Gardner* and *Lyon* 1977). Each of these is a population characterized by specific sexual, biologic, cultural, and ethnic variables. An earlier report (*Jordan* et al. 1969) speculated upon the low frequencies of cervical cancer in American Indian women of New Mexico, and ascribed them to a period of sterility during adolescence which resulted in delay of first pregnancies. However, alternate explanations might include such factors as lower life expectancy for American Indians, and the large number of these women who might not have reported their condition to the Health Service, where this information was obtained.

It is well known from the work of *Oettle* (1964) and others that rates of cervical cancer for African blacks vary from tribe to tribe and from region to region. In South Africa rates comparable to those of American black women have been reported as among the highest in the world. Pathologies ranging from dysplasia to invasive carcinoma occur frequently among the Tswana women of South Africa (*Fragoyannis* et al. 1977). High incidence and death rates have also been reported among inmates of women's detention facilities in the United States, prostitutes, and urban women (*Martin* 1967). The international literature is extensive and earlier individual reports are summarized elsewhere (*Rotkin* 1967a).

On a worldwide basis, cervical cancer is the most prevalent of all female-limited neoplasms, exceeding those of the breast and the reproductive system. However, in some populations, especially those of the United States and Europe, rates of endometrial cancer have risen dramatically and, with the general reduction of cervical cancer mortality rates in the developed countries, have even exceeded the former in some populations.

Table 1 presents incidence and mortality rates for selected worldwide populations; only those countries for which both measures are available are included. The use of mortality data to determine the true extent of cervical cancer in any population is questionable since survival for cases treated early can be quite high, amounting to 70% or more of cures for stage 1 lesions with good provision for diagnosis and care, and fairly high even for more advanced cases. In developing countries, where access to

Table 1. Selected worldwide incidence (1967–1971) and mortality (1974–1975) rates of cervical and corpus cancers per 100 000 women, adjusted for all ages [a]

Population	*Cervical cancer*		*Corpus cancer*	
	Incidence	Mortality	Incidence	Mortality
Colombia	62.8	5.6	5.1	4.9
German Democratic Republic	33.2	14.3	13.0	8.5
New Zealand	31.0	5.8	10.0–22.3	3.9
Singapore	11.6–29.3	5.8	2.9– 4.9	1.5
Peru (Lima)	28.6	12.7	3.1	2.1
Rumania	26.3	11.7	8.8	8.5
Puerto Rico	25.6	4.0	6.1	5.6
Japan	13.8–24.9	2.9	8.1	7.4
Canada	10.5–22.6	4.9	9.0–17.4	4.2
Norway	18.1	8.9	9.7	5.0
Yugoslavia	18.1	4.9	9.1	8.7
Sweden	17.7	6.9	12.1	7.9
United States, all races	17.3	5.5	19.3	5.6
Switzerland	16.1	5.9	16.3	8.8
United Kingdom	10.1–16.1	6.3–8.8	6.7–11.0	6.8
Hungary	11.0–16.0	9.8	7.0–12.3	16.0
Israel (Jewish)	4.5–5.0	2.3	10.8	4.0

[a] Sources: Incidence rates (except Peru), *Cancer Incidence in Five Continents* (1976). Mortality rates (except Peru), *World Health Statistics Annual* (1977). Peru, *Brandon* (1973)

care is limited, many cases will not be discovered, and death records often will not carry cancer as a first, or perhaps any, cause. For these reasons incidence data are preferred, assuming that an adequate population base is available, but this is often difficult to ascertain. For many countries only mortality information is available. Rates for the countries represented in Table 1 are given as the number of new cases and deaths reported in 1975 from the total population of women of all ages. For some countries two rates are shown to represent a range from different reports.

The extremely high incidence rates in developing South American countries, and the continuing low rates among Jewish populations in Israel and elsewhere, have been described. Other very excessive rates are found in the United States nonwhite population, West Germany, New Zealand, Singapore, Rumania, Puerto Rico, Japan, and perhaps Canada. Rates for Norway, Yugoslavia, Sweden, the United States white population, Switzerland, the United Kingdom, and Hungary are not as high, but are still substantial. Mortality as a proportion of incidence varies from the exceptionally low rate in Colombia to approximately half of all cases in Israel, Hungary, Norway, and the United Kingdom.

Comparison rates for endometrial cancers are also shown in the same table. Legend has it that corpus cancers are a small fraction of all uterine carcinomas, perhaps 25% or less, but recent information indicates a sizable departure from this view. Highest incidence rates are found in the developed countries: the United States, New Zealand,

Switzerland, West Germany, Hungary, and Israel. The most severe death rate is found in Hungary, where mortality is higher than incidence, which is explained by the accumulation of cases from the past in 1 year and reflects a decreasing incidence in that country.

Figure 1 presents morbidity rates in declining order to illustrate the lack of relationship of death rates to diagnosed cases in 1975. The ratio of mortality to morbidity indicates the remarkable range of 8% who died in Columbia to 61% in Hungary.

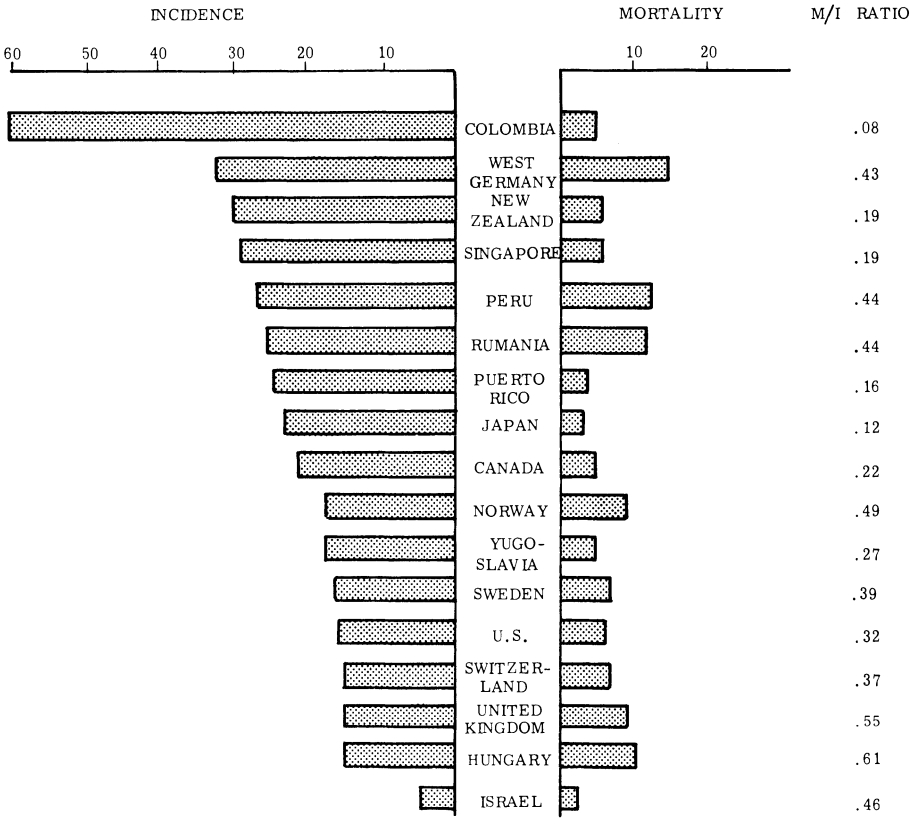

Fig. 1. Incidence rates of selected worldwide countries in descending order of frequencies and corresponding mortality rates for the same populations. Mortality trends do not follow those of incidence. The M/I (mortality/incidence) ratio provides a relative measure of survival by estimating the proportion of cases that died, possibly attributable to the effectiveness of programs of early detection. However, note that some of the developed countries have the highest ratios, whereas in other developed countries they are extremely low, as in Japan. Unless carefully viewed, the M/I ratio can be misleading because it does not indicate the full extent of cervical cancer in a population. For example, Colombia, with the lowest ratio, has the highest known incidence, compared to Israel with a very high ratio but with the lowest known incidence, where very few Jewish women are diagnosed with cervical cancer, but of which about half result in mortality. Sources: incidence rates (except Peru), *Cancer Incidence in Five Continents* (1976); mortality rates (except Peru), *World Health Statistics Annual* (1977); Peru, *Brandon* (1973)

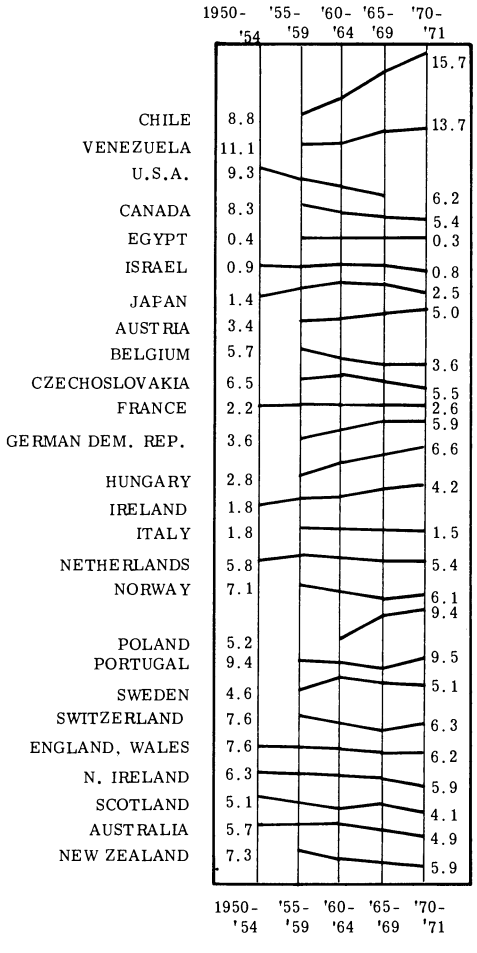

Fig. 2. Trends for worldwide mortality from cervical cancer, 1950–1971, age standardized as rates per 100 000 women. See text for details. Source: *Hill* (1975)

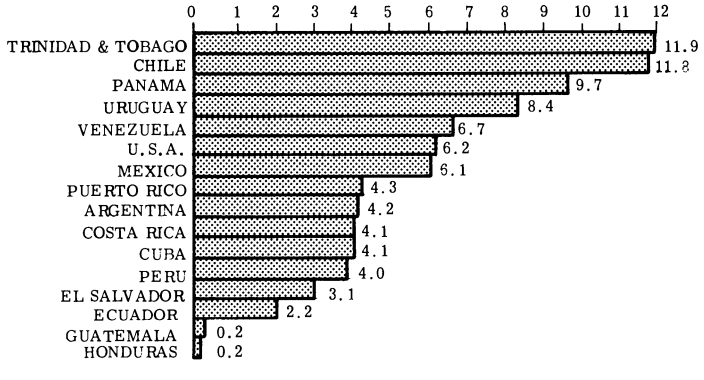

Fig. 3. Cervical cancer mortality rates per 100 000 population of all ages in selected Latin American countries. Source: *World Health Statistics Annual* (1977)

Mortality trends from 1950 through 1970 covering selected countries in five continents are shown in Fig. 2. Inspection of these trends demonstrates generally that death rates from cervical cancer have remained static or are decreasing in most developed countries, but with some striking exceptions in West Germany, Hungary, and Ireland, as well as in the developing coastal countries of South America. Death rates in the United States and Canada have sharply declined during most of this period.

The focus of Fig. 3 is mortality from cervical cancer in countries of Latin America for 1971–1972. The United States, a developed country, is included for comparison. Although not shown, death rates for Colombia, where incidence is highest, are about the same as for Mexico. Again, these mortality rates reflect such confounding variables as life expectancy, access to medical diagnosis and care, levels of deprivation, and other influences upon the proportions who die from cervical cancer, rather than on numbers of new cases each year.

Between 8000 and 12 000 women still die annually from cervical cancer in the United States, with estimates depending upon the source of the information. The incidence rate for white women, 1969–1971, was less than half that of 1947–1948, a trend generally found in other developed countries; but mortality for white women did not decline appreciably from 1947 to 1969, as shown in Table 2. Shown also for

Table 2. Comparison incidence and mortality rates per 100 000 females for various cancer sites in white females in the United States [a]

	Incidence		*Mortality*	
	1947–1948	1969–1971	1947–1948	1950–1969
Breast	72.6	75.0	27.2	25.5
Colon	34.2	29.4	18.1	16.2
Cervix uteri	32.8	15.0	8.5	7.8
Corpus uteri	16.0	21.0	1.6	6.1
Ovary	14.9	14.3	9.2	8.6
Rectum	14.4	10.6	5.4	4.8
Stomach	12.0	6.8	8.6	7.7
Lung	7.2	14.4	5.9	6.3
Mouth and pharynx	6.3	5.6	1.7	1.1

[a] Sources: 1947–1948, incidence and mortality, *Dorn* and *Cutler* (1959). 1969–1971, incidence, *Cutler* and *Young* (1975). 1950–1969, *Mason* and *McKay* (1975)

comparison in this table are other cancers occurring with greatest frequency in women in the United States, excluding skin cancers. The decline of cervical carcinomas is paralleled in the United States only by rates of stomach cancer. Except for endometrial and lung cancers, both of which have increased in frequency, all other cancers show relatively the same rates over more than 2 decades; only corpus cancer has resulted in markedly greater mortality. It is difficult to explain why death rates from cervical cancer should remain so high despite greatly reduced incidences, and why mortality from corpus cancers should have risen so dramatically in a developed country. Both cancers are readily detectable, in the cervix more so than in the corpus, in early stages. *Beral*

(1974) has reported elevated death rates from cervical cancer among *young* women in Britain between 1970 and 1976, confirmed by *Yule* (1978), possibly reflecting a separate lesion which progresses rapidly or a generally accelerated latency period for some unknown reason, with deaths resulting from an often voiced reluctance to perform surgery. A similar trend was recently reported for parts of Scotland by *MacGregor* and *Tepper* (1978), who concluded that such a general trend would not take place in the presence of maintained screening programs, a conclusion based on data showing reduced rates in Scotland where such programs are established.

Black women in the United States comprise one of the highest risk groups in the world, with an average incidence and mortality more than twice that of white women in the nine United States populations studied by *Cutler* and *Young* (1975), Fig. 4. The black to white ratios range from an excess of 50% to almost 200% more black women

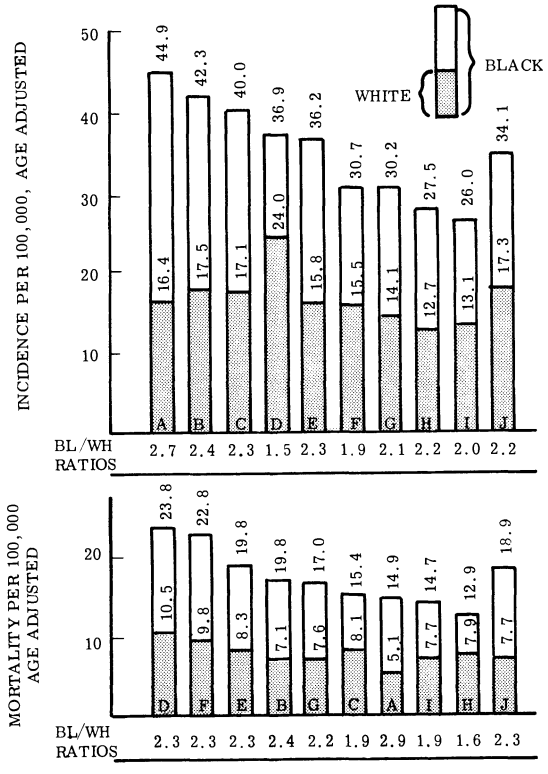

Fig. 4. Comparison rates and ratios for incidence *(upper)* and mortality *(lower)* from cervical cancer in black and white women (BL/WH) of nine regional United States populations. Each geographic area in both charts is designated by the same letter as follows: *A*, Minneapolis; *B*, Iowa; *C*, Dallas; *D*, Birmingham; *E*, Detroit; *F*, Atlanta; *G*, Pittsburgh; *H*, Colorado; *I*, San Francisco; *J*, the United States. Iowa and Colorado are states, all others except the United States are SMSAs (Standard Metropolitan Statistical Areas). Sources: Incidence, *Cutler* and *Young* (1975); mortality, *Mason* and *McKay* (1975)

who are diagnosed with and die from cervical cancer; however, the ratios of incidence to mortality, shown in Table 3, are quite constant for whites and blacks, perhaps indicating similar levels of care and survival rates in the cities and states under study.

A comparison of incidence rates spanning more than 20 years, 1947–1948 to 1969–1971, for whites and nonwhites in the United States shows an equivalent decline in cervical cancers for both races, although there are still twice as many cervical carcinomas among nonwhites as among whites (Table 4). But, whereas corpus cancers have doubled in white women in the United States, corpus cancers in nonwhites

Table 3. Incidence/mortality ratios for cervical cancer in white and nonwhite females in the United States, in nine selected representative regional populations [a]

	Ratios	
Population	White	Black
Minneapolis	3.1	2.9
Iowa	2.4	2.4
Birmingham	2.2	1.5
Dallas	2.1	2.5
Detroit	1.9	1.8
Pittsburgh	1.8	1.7
Atlanta	1.6	1.3
Colorado	1.6	2.1
San Francisco	1.6	1.8
$\bar{x}$ (Means)	2.0	2.0

[a] Derived from data by *Cutler* and *Young* (1975)

Table 4. Comparison age-adjusted incidence rates per 100 000 white and nonwhite United States women for cervical and corpus cancers, 1947–1948 and 1969–1971[a]

	1947–1948		*1969–1971*	
	Cervix	Corpus	Cervix	Corpus
White	32.8	10.3	15.0	21.0
Nonwhite	70.4	11.2	33.8	12.1

[a] Sources: 1947–1948, *Dorn* and *Cutler* (1959). 1961–1971 *Cutler* and *Young* (1975)

have not increased. That this would indicate separate etiologies for both cancers in whites and blacks is moot; perhaps more relevant is the generally held notion that the white population in the United States is developed and that the black population is developing. The reduction of incidence from 1947 to 1971 in both races is shown dramatically for six large cities in Fig. 5; the exception was San Francisco, where a surge of incidence in blacks seems to have taken place. In all cities, however, there is substantially more incidence in blacks than in whites. Trends in Birmingham, Detroit, and Dallas also show an upturn around 1970.

Etiology and Pathology. In his earlier work, *Dunn* (1958) presented the concept that the invasive form of cervical cancer develops from the in situ lesion; in later publications he espoused the notion of continuous development from the earlier dysplasia

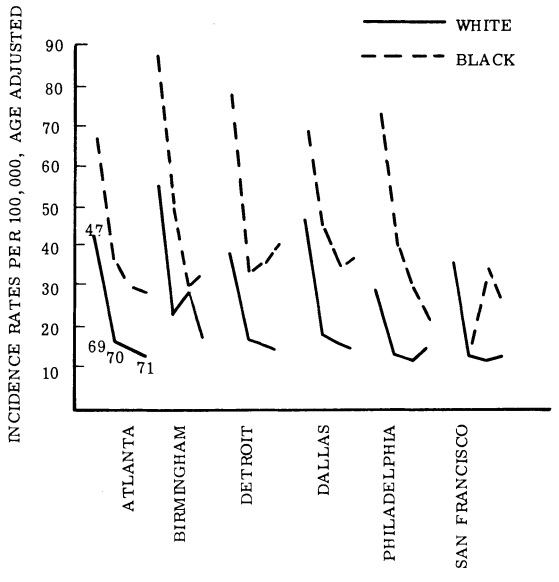

Fig. 5. Cervical cancer incidence trends, 1947–1971, in six United States cities. See text. Source: 1947, *Dorn* and *Cutler* (1959); 1969, 1970, 1971, pers. communication, unpublished data from the *Third National Cancer Survey of the Biometry Branch,* National Cancer Institute

through the in situ and into successive invasive stages. That such a morphogenesis of cervical cancer in humans could be adapted to the animal model for carcinogenesis, as developed by *Berenblum* (1941) from his own and preceding observations, was not proposed until the 1960s (*Rotkin* 1962, 1967a), modeled later as an ordered sequential progression (*Rotkin* 1972) (Fig. 6), based upon strong epidemiologic evidence identifying the effect of sexuality upon active adolescent tissue as a key event leading to the oncogenic transformation of cells at risk.

The hypothesis of sequential development, especially that the invasive lesion derives directly from the in situ stage, was questioned in a much-quoted British publication (*Knox* 1966) requiring substantial evidence that such a developmental sequence actually takes place. Although *Knox* expressed a largely overlooked conviction regarding the probability of such a sequence, his demand for proof resulted in the widespread rejection of cytologic screening for early detection of cytopathologic abnormalities which, in theory, could develop into an invasive carcinoma.With a focus on long-term screening programs such as the one conducted in British Columbia, accumulating literature thereafter purported to demonstrate that although mortality from cervical cancer had generally decreased in certain populations, the widespread utilization of cytologic smear tests had not materially affected such a trend. These studies covered a period of time hardly long enough to produce conclusive data.

Following identification of key risk variables for cervical cancer (*Rotkin* 1962, 1967a), a search for sexually transmissible oncogenic agents took place, with several communicable candidates being proposed. The common denominator for all such possible agents was the assumption that extraneous DNA was contributed to the female at risk by the male sexual partner, with the ensuing mutagenic change providing an acceptable condition for carcinogenesis. That this universally believed provision for alteration and reassembly, or loss or gain of chromosomal nucleotides, had not been demonstrated on a reasonably secure level did not arise as a deterrent, although other mechanisms for continuous and aberrational division of cells exist.

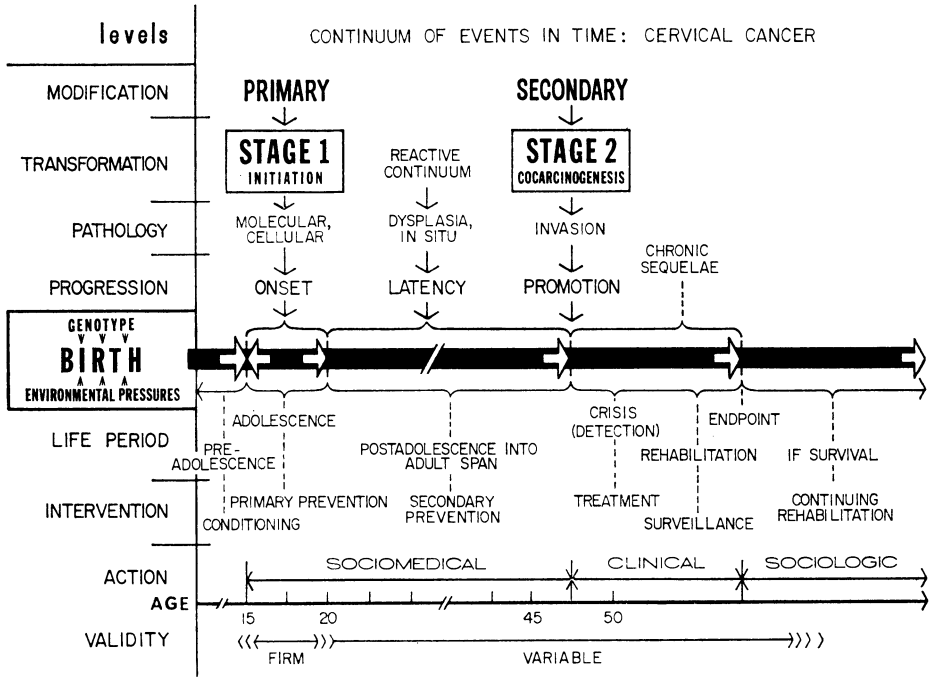

Fig. 6. Model of carcinogenic events from initiation through the latent period and leading to invasive cervical cancer. The *heavy horizontal bar* (with *arrows*) represents the lifeline as it originates at conception and birth. Above the lifeline are levels describing the continuum of developing cervical carcinoma as they fit the multistage model of carcinogenesis, latency, and cocarcinogenesis. Below the lifeline are levels associated with control of cervical cancer as it conforms to the multistage continuum. Events in time are scaled by age of the candidate at risk at the bottom. Reproduced from *Rotkin* (1972) with permission of author and publisher (Springer-Verlag)

It is not the purpose of this chapter to discuss detailed pathologic changes in the cervix leading to cancer, yet it is difficult to separate those disciplines serving an understanding of the disease (epidemiology, demography, statistics, and pathology) from gynecologic partice, molecular and animal investigations, and, more recently, virology, immunology, and genetics. *Knox* required elaborate field studies to verify the transition from early cellular abnormalities to malignancy, yet evidence is already accumulating that the model is real. *Johnson* et al. (1968) presented information suggesting that carcinoma in situ can develop from dysplasia during a period of recurrence; and *Noda* (1976), following a series of dysplasias and in situs, reported that 66% of the latter progressed to invasion and 15% of severe dysplasias progressed to in situ and invasive lesions, but that most cases of mild dysplasia disappeared within 18 months. It would seem, perhaps, that some of the early pathologies were different from those that continued to develop.

The important question is: What proportions of dysplasis regress and and progress? *Stern* (1969) has shown a progression rate of 5–6.4% per year. Regression rates of about one-third have been reported, but with a high rate of recurrence thereafter (*Stern* and *Neely* 1964). Since some lesions can be shown as progressive and others as

regressive, the issue is: Are both dysplasias the same? Following *Reid*'s earlier studies, *Coppleson* and *Reid* (1968) and *Coppleson* (1969) examined the morphology of squamous cervical epithelium and presented a set of views regarding cellular activity phases leading to carcinoma. Their position was that in contrast to the normal process by which columnar cells are transformed into squamous epithelium, an atypical metaplastic alteration of special columnar cells, which replace those of normal columnar epithelium, takes place and results in dysplastic tissue, which is capable of becoming neoplastic. The episode of metaplasia is regarded as a dynamic process during which oncogenic transformation may take place. The time of life when metaplastic activity is greatest is adolescence, confirming findings that early adolescent coitus is a period of heightened vulnerability (*Rotkin* 1962,1967a). They further reported that the atypical type of metaplasia can rarely be found in the virgin, whereas it is common in the sexually active adolescent girl. Additionally, they reported a period of squamous metaplastic activity associated with the first pregnancy. The origin of the new epithelium following metaplasia is regarded as being derived from stromal cells, not from reserve cells, as had often been held. Once transformed, these epithelial cells are phagocytic and are able to accept and metabolize available materials. These authors prefer to believe that the essential material taken up that leads to carcinogenesis is one form or another of nucleic acid. Such a component would be delivered by the male sexual partner, who operates as a vector delivering an agent. Several such agents are under consideration: spermatozoa from deposited semen and herpes virus type 2. Considered also in the past, before the theoretical period, were infectious bacteria and certain protozoa associated with the genitalia. Adherence to a preference for transformation by nucleic acids excludes the possibility of a chemical or hormonal etiology. Although the latter is highly unlikely, and despite some unjustified effort in such an endogenous direction, the possible effect of a metallic ion or a carcinogenic substance cannot be set aside.

It seems fairly secure that demographic, epidemiologic, etiologic, and pathologic findings point to an increased risk of highly active young cervical epithelium, at least of certain cells which are possibly programmed genetically to become atpyical, and to develop changes leading to malignancy, provided the pathologic continuum is accepted. Established concepts of carcinogenesis, so convincingly demonstrated in laboratory animals, require four ordered sequential conditions for a solid carcinoma to arise and develop: availability of vulnerable tissue in the young animal, application of a carcinogen, a long latent period, and a cocarcinogen (second carcinogen) applied to the same tissue. The findings of rising death rates in young women in the several cited British reports raise the possibility of two separate types of development: one following the dogma of carcinogenesis with a long latency period, and the other developing directly from an innocent but identified metaplastic epithelium into an invasive lesion after a very short latency or by skipping intermediate stages of development. Thus, it is possible that a stage 1, in situ, dysplastic or earlier precursor can be promoted directly into a stage 3 or 4 lesion, a kind of fulminating development resulting in excessive death rates in young women.

The concept is not new, *Dunn* (1958) having sensed that some cervical malignancies progress from negative cytology to an early invasive cancer within a year. From studies of the Connecticut Tumor Registry in the United States, *Laskey* et al. (1976) have

presented additional evidence to indicate that some women diagnosed with an early localized disease died quickly thereafter; they conjectured that in these cases the carcinoma developed rapidly whereas others did not, providing evidence for two classes of invasive cervical cancers. The argument might be made that faulty diagnosis, not unusual in assessing early stages of cervical cancer, might account for those cases, and that they might have been more advanced when first discovered. However, earlier notions of growth patterns may be useful in explaining dual development: on the one hand, that cervical cancer develops in the basal layer of squamous epithelium, the cancer cells immediately becoming capable of invasion by breaking through the basement membrane and infiltrating the underlying stroma; and on the other hand, that cancer cells grow from the basal layer toward the surface stratum of epithelium, and that invasion of the stroma does not take place until after the latency period. The contrast is that of monophasic growth by direct invasion against biphasic growth in two stages over time. *Madej* (1965) described observations over a 10-year period which seemed to support the hypothesis of monophasic development in a number of cases. Although the *Reid* group departs from these earlier beliefs in proposing a special type of columnar epithelium which undergoes squamous metaplasia, their model can be adapted to both monophasic and biphasic growth patterns simply by collapsing or extending the time of development, since later stages, particularly those normally following the latent period, are skipped. However, the additional provision would be that two different types of cells are required, one branching in the direction of long development, the other going directly to invasion. For this, a genetic difference might be considered.

Risk. Surveys, some already cited, are available which document and discuss the purported associations with increased risk of cervical cancer which have arisen since the time of *Rigoni-Stern.* Table 5 lists most of these variables, arranged into content-coherent groups (domains), and with unavoidable overlap between groups and variables. Each variable carries an appraisal of relationship to increased risk of cervical cancer, as derived from the literature.

Sociocultural Definers. The candidate at increased risk of cervical cancer is profiled as a woman with origins in deprivation, probably black, Hispanic, East Indian, or Puerto Rican, but also including whites in lower economic classes and excluding certain religions (*Rotkin* 1972). That this invariably has been the case is well demonstrated by incidence rates in developing countries and also in disadvantaged population segments in both rural and urban settings of developed countries. It must be stressed that different classifications of race, religion, economic status, education, and occupation do not in themselves directly confer different degrees of risk upon cervical tissue, although many studies have demonstrated such relationships. The cultural gradient was explored by *Clemmesen* (1951); later studies confirmed that incidence rates rose as the social class descended, with highest risk occurring among the poorest and least educated (*Graham* et al. 1960; *Lundin* et al. 1964). Later case-control studies confirmed this, not only with regard to income levels, but also with numbers of family dependents, occupation of the patient and her husband (*Rotkin* and *Cameron* 1968), and even sibling order where the patient was found to be a middle child, and presumably less favored than the oldest and youngest children (*Rotkin* 1972).

Table 5. Summary of variables proposed and/or studied for relatedness to risk of cervical cancer, grouped and assessed

Domains, with defining variables	*Outcome,* relatedness to risk
Sociocultural	
Race	Increased risk: nonwhite
Religion	Decreased risk: Jewish, Amish, Mormon, Nuns
Economic status	Increased risk: poverty, deprivation
Education	Increased risk with less education
Migration patterns	Not studied
Marital	
Marriage	Increased risk
Age at first marriage	Increased risk with early marriage
Multiple marriages	Increased risk
Broken marriages/separations	Increased risk
Sexual	
Celibacy	No risk
Age at onset of coitus	Increased risk with early onset, key variable
Number of sexual partners	Increased risk with more, key variable
Frequency of coitus	Not related
Coital practices: positions, type	Not related
Unstable sexual relationships	Increased risk with premarital, extramarital
Prostitution	Extreme risk
Reproductive	
Nongravidity/nonparity	Not related; no risk with celibacy
Gravidity/parity	Relatedness by number not demonstrated
Menses	Not related
Contraception: barrier, IUD, oral	Barrier, decreased risk; others, not resolved
Sterility	Increased risk doubtful, one study positive
Traumatic	
Abortion	Not related
Injury: postpartum or from glans	Not related
Ritualistic	
Niddah, practiced by Jewish women	Not related
Exogenous	
Noncircumcision in coital partners	Not related by itself
Transmissible agents: sperm, HSV 2, monilia, trichomonas, venereal diseases, chemical carcinogens, metallic contaminants, others	Not resolved; possibly all are related
Genital hygiene	Not resolved
Diet	Not studied
Administered hormones, medications	Little information
Coal tar douches	Some evidence for increased risk

Table 5 (continued)

Domains, with defining variables	*Outcome,* relatedness to risk
Endogenous	
Genetic	Not resolved; in conventional studies, not related
Hormonal	Probably not related, no convincing evidence
Personality/psychosocial	Not resolved
Institutionalization: nuns, detained populations	Nuns, no risk; Inmates, extreme risk
Adolescence (teenage)	Direct risk variable, includes key variables
ABO, Rh blood groups	Not related
Pathologic	
Cellular morphology (carcinogenesis)	Progression of stages: dysplasia, in situ, invasion: demonstrated, but some ca's may skip in situ
Squamous metaplasia	Related to adolescence
Commonality of etiology: cervix, prostate	Not demonstrated
New hypotheses	
Specific proteins, surface DNA	Theoretical, proposed from lab material
T. vaginalis	Proposed, not resolved
N-nitrosamines	Proposed, not resolved
Smoking	Some evidence, not secure

Other studied indicators have also attempted to emphasize the association of low sociologic position with increased risk, but the long-sought biologic commonality with direct effect upon oncogenic transformation of cervical epithelium is sexuality (*Rotkin* 1962, 1967a). Sociologists have repeatedly demonstrated the apparently linear correlation of earlier sexual onset with lower social status. As the population becomes poorer and less well educated, coitus occurs at younger ages for a number of reasons: peer pressures, male urgencies, shorter periods of dependency upon the family, lack of parental guidance, forced early maturity, and failure for employment and constructive involvement to develop, with sexuality seen as a major replacement for other activities and values. Sexuality is also a marketable service, containing the promise of rewards for the young girl in many cultures: money, acceptance, protection, companionship, even upward mobility into higher social classes where cervical cancer is also related to early coitus. It is for these reasons that female children become available in the *barriadas* of South America, that girls become sexually involved at very young ages in the inner cities of United States metropolitan areas, and that coital precocity takes place elsewhere in the world under similar conditions.

Marital Events. That the marriage ceremony, with license and blessing, delivers a carcinogenic curse to the cervix is difficult to believe, yet study after study, beginning with those of *Rigoni-Stern* in 1842, has demonstrated excessive risk of cervical cancer for

women who are married, who were wedded early in life, who had several husbands, and whose marriages resulted in divorce or separation (*Jones* et al. 1958; *Aitken-Swan* and *Baird* 1966; *Rotkin* 1973). The nuptial bed is the variable with direct biologic relevance, particularly if visited for the first time at an early age when cervical tissue is vulnerable to sexually introduced oncogenic contaminants. Separations can encourage infidelity, and broken marriages often result in postmarital sexual adventures and new husbands, all diverse events with the same outcome of additional sexual partners. Where early marriage is traditional, as in parts of the Orient, incidence rates of cervical cancer would also be expected to rise, as a consequence of cultural practice and not necessarily as an outcome of social status.

Sexuality. Studies continue to accumulate in overwhelming support of the two sexual variables, early coitus and multiple partners, originally identified as central to virtually all other hypothesized factors. These have now been reported in a number of additional populations: Nigeria (*Adelusi* 1977); Zambia (*Naik* 1977); young women of England and Wales (*Yule* 1978); Tokyo (*Masabuchi* and *Nemoto* 1972); Barbados (*Barron* and *Richart* 1971), high frequencies of cervical cancer among worldwide detained and prostitute populations where most women had experienced coitus very early in life (*Keighley* 1968; *Audet-Lapointe* 1971; *Singer* 1975a; *Sebastian* et al. 1978), in addition to earlier prison studies showing similar results (*Pereyra* 1961; *Moghissi* and *Mack* 1968); a generalized concensus among reviewers (*Harington* 1977; *Canadian Task Force* 1976; *Coppleson* 1969; *Rotkin* 1967a, 1973); and increasing rates of abnormal cytologic findings in adolescent girls (*MacGregor* and *Tepper* 1978; *Andrews* et al. 1978; *Meisels* et al. 1977; *Feldman* et al. 1976; *Wallace* and *Slankard* 1973; *Kaufman* et al. 1970). Additional new evidence was reported in two populations where cervical cancer rates are exceptionally *low:* among Mormon women of Utah (*Gardner* and *Lyon* 1977), where the birth rate is highest, yet where incidence is lowest in the United States, and where strict codes of behavior result in comparatively late marriage without previous sexual experience; and also among women of aborigine Malaysian Orang Asli (*Sumithran* 1976) where sexuality outside marriage is taboo. In the face of mounting epidemiologic and pathologic evidence, the designation of coital onset during adolescence as a pivotal variable increasing riks (*Rotkin* 1962) seems increasingly secure.

A histologically demonstrated squamous cell carcinoma of the cervix was recently described in a *married* 58-year-old "nulliparous" menopausal British virgin (*Mogaji* 1973), the first such case to be reported. Verification of virginity was assumed from the almost imperforate hymen, no premarital history of sexuality, and lack of marital consummation. The information is much more believable than the occasional cases of cervical cancer in children, assumed virgins, ratios of cervical cancers in virgins to non-virgins, and nuns. Despite this single case, there is no question but that celibacy confers virtually perfect protection against cervical cancer, although large enough numbers of celibate women to provide an expected frequency of cancer have not yet been investigated.

As numbers of sexual partners accumulate, particularly during adolescence, so also does risk increase (*Rotkin* 1962, 1967a, 1972). Since virgins are exempt from risk, it is assumed that the male sexual partner contributes an oncogenic organism or carcinogenic

substance to cervical tissue at the time of life when this tissue is most active and vulnerable, each male being regarded as a possible carrier of a transforming agent. It is for this reason that *Keighley* (1968) concludes that cervical cancer is "one of the most serious occupational hazards" for prostitutes, an observation based on several studies (cited earlier) reporting highly excessive numbers of dysplasias, in situs, and invasive cancers in detained women, most of whom are characterized as "prostitutes" or "promiscuous."[2] Especially important is the finding that virtually all women in these classifications had adolescent sexual beginnings.

Some recent researchers have divided the integrated model for carcinogenesis into two separate hypotheses, one relating risk to early age at first coitus, the other stressing variables associated with multiple sexual partners (*Beral* 1974; *Sumithran* 1976). This an unfortunate misinterpretation of the full theory (*Rotkin* 1967a, 1972), which regards adolescence as a period of greatest susceptibility to initiation of neoplasia, perhaps as an end result of squamous metaplasia, and provides, further, that each additional sexual consort increases the probability that a contributed agent will be encountered which can engender such epithelial changes. The two conditions are associated in the same general process, which is not exclusively limited to the period of adolescence; there is the theoretical possibility that this chain of events could occur at any time in life. Still, partitioning of the theory has led to an examination by some workers of the effectiveness of multiple sexual partners as the primary variable. In one study of Jewish women in Israel (*Pridan* and *Lilienfeld* 1971), data were not considered which clearly demonstrated earlier onset of coitus by patients compared to controls; the authors favored numbers of sexual partners, possibly because the theoretical synthesis of both variables on the basis of accumulating data (*Rotkin* 1967a, 1972) was not then explicit. *Singer* (1975a) has recently focused upon the effect of "promiscuous" sexual activity on the transformation zone of the cervix, as evidenced by large areas of metaplastic squamous epithelium compared to the virginal cervix showing very little change, and showing also an early onset of coitus among women inmates with major cervical abnormalities.

The large literature on coital frequencies fails to demonstrate any consistency of trend and presents no reason to believe that excesses or deficits of sexual acts for any given period are related to increased risk (*Rotkin* 1973). Where studied, the diversity

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2 The use of quotation marks around these two words results from my wish to avoid judgmental verbiage. It is difficult to establish the specific number of sexual partners required to label a woman as "promiscuous," an offensive, accusatory term. Many "respectable" women have experienced considerable numbers of sexual partners, yet the word "promiscuous" is not applicable because they are discreet, nor is the term used to identify women who have been married many times. The term "prostitute" is also condemnatory and refers only to the practice of accepting payment for a sexual episode, not too different from gifts, meals, and other favors tendered universally by men to women in and out of marriage, where the outcome also includes the sexual act. The common denominator is something of value received for coitus, among other advantages. I use these terms because they are so prevalent in the literature, but better usages might be "multiple sexual partners," now widesread in the literature, and "sexual professionals." The relationship to cervical cancer is that more than one sexual partner increases risk, and that as numbers accumulate, each additional male is a possible carrier.

of coital practices such as positions, oral and anal acts, and other aspects of sexual mechanics, does not appear to influence risk (*Rotkin* 1967b). When summarized and compared, a number of studies have reported excesses of cervical cancer patients with instabilities of marital and sexual patterns, but it has been pointed out that the biologic implication of such behavior is increased motivation and opportunity for sexual relations with numbers of partners. From all this, it would seem that in what way and how often the sex act is performed have no bearing upon risk.

Reproductive Associations. Coppleson (1969) has described areas of developing squamous epithelium in women with first pregnancies similar to those found in coitally active adolescents, but epidemiologic studies so far have failed to implicate gravidity and parity as epidemiologic variables increasing risk; this lack of effect during pregnancy results possibly from a compensatory development of protective systems, perhaps immunologic. Where large numbers of pregnancies are found, there is invariably a concomitant earlier age at time of marriage and/or onset of sexuality. This complex question is discussed by *Singer* (1975b) in relation to etiology, but it cannot yet be concluded from comparison frequencies of gravidity and parity in relation to cervical cancer that a risk association exists, except in the case of celibate women, where nulliparity is not the issue. From the observations of *Coppleson* and *Singer,* there is reason to propose pregnancy as a time of vulnerability to initiation of the carcinoma, but from available data the conclusion still must be that other physiologic currents appear to hinder establishment of the lesion. This entire area should probably be aggressively pursued.

Several studies of menstrual function have revealed no differences between patients and controls for mean age of menarche, duration of menses, interval between menses, and irregularity. In only one study (*Kessler* et al. 1974) do differences arise, but with excesses of abnormalities favoring controls, perhaps reflecting a chance effect or methodologic problems, especially since all other carefully controlled studies found no such differences (*Rotkin* 1973).

A few studies suggest that a barrier contraceptive method may reduce risk of cervical cancer, a finding supported by a recent report (*Canadian Task Force* 1976) containing evidence that risk is lower for women using barrier methods than for those who use oral contraceptives. This report declares that no evidence yet exists showing that oral contraceptives have "a direct carcinogenic effect on the cervix." A California study (*Peritz* et al. 1977) found a 3-to-5-fold increase in risk of cervical cancer for women using oral contraceptives, this result persisting when total dysplasias were included with carcinomas. However, the effect was *negative* for severe dysplasias. A Canadian study (*Meisels* et al. 1977) reported a significant excess of dysplasias in oral contraceptive users, but also a strong correlation of such use with early onset of coitus.

Literature on the effect of intrauterine devices (IUD) for contraception has not yet accumulated. One recent study conducted in India (*Luthra* et al. 1977) reports no significant progressive cytomorphologic abnormalities from the use of copper devices. It may be said for both oral and IUD methods that in view of the long average period of latency required for cervical cancer to develop, and of the maximal effect of adolescence upon initiation, large populations of women who began to use these methods early in life would be required for study. Only now would some cases of cancer perhaps begin to appear.

Sterility has been examined in one study of American Indian women (*Jordan* et al. 1969) as a factor increasing risk. A delay in first pregnancies among these women was ascribed to a "period of transient adolescent sterility;" consequently, age at first childbirth appeared more strongly related to the development of cervical cancers than age at first coitus, these women having been found with a lower rate of cancer than matched Caucasian controls. This report provides no information on the life expectancy of these women, nor on how many were not diagnosed.

Traumatic Episodes. Where damage to cervical tissues can be expected from induced or spontaneous abortions, from thrusts of the glans penis, or from postpartum lacerations, available information appears to rule out these injuries in relation to increased risk (*Rotkin* 1973). *Masters* and *Johnson* have demonstrated through movies that the cervix recedes into the false pelvis during sexual intercourse, providing little opportunity for the glans to become aggressively harmful. Evidence of tears and bruises from natural childbirth is extremely difficult to control, since many women experience these injuries without a follow-up examination, especially in developing countries and deprived populations. Such an effect upon the risk of cancer has never been demonstrated.

Exogenous Influences. The ascribed relationship of noncircumcised sexual partners to the risk of cervical cancer has run its course and has been found wanting. Levels of energy and enthusiasm for this hypothesis easily ran as high as those for herpes simplex virus type 2 today, yet careful analysis of major circumcision studies (*Rotkin* 1973) has demonstrated that not one provided evidence for such an association; in fact, the evidence was contrary in trend. New observations have largely discouraged the resurrection of noncircumcision as a risk variable (*Terris* et al. 1973; *Naik* 1977; *Emovon* 1977). Smegma under the prepuce was identified as the active carcinogen, based upon animal experiments which were also negative or indecisive. The impetus for this belief was originally derived from low frequencies of cervical cancer in Jewish women, all of whose husbands were circumcised. Acceptance of the oncogenic power of the prepuce has now been abandoned, but establishment of the high-risk male remains a reality. However, the direction taken by current studies to identify these males is disappointing.

One such study (*Kessler* 1976) investigated the previous wives of husbands whose current wives were found to have cervical cancers. An excessive number of cervical cancers were found in previous wives. Studies of this type require assessment of *all* sexual partners of previous wives, since these women will have had succeeding husbands, and there is a fair probability that between marriages they will have experienced additional sexual partners, each of whom contributes the additional likelihood of being the carrier of an oncogenic agent. The study also suffered from incompleteness, since only a small percentage of subjects were followed, a difficulty inherent in studies of this type.

Singer et al. (1976) have proposed an extension of *Reid*'s hypothesis implicating basic proteins in the sperm head. Specifically, they point to certain histones and protamines as the oncogenic fractions which are effective upon surface DNA-containing filaments of the cervical metaplastic cell, the high-risk male presumably departing from the normal by the amount or structure of these gametic proteins – an interesting

new consideration. There is no doubt that identification of high-risk males would serve to confirm the effect of transmissible agents upon initiation of cervical cancer, and that this identification should be pursued; but small samples of males ascertained to be sexual partners of cervical cancer patients, and a follow-up of all sexual consorts of both males and females would be more productive than large, incompletely researched studies only on spouses.

Nor has herpes simplex virus type 2 (HSV2) convincingly been identified as an oncogenic agent. There are too many inconsistencies of assay methodology and results in the swiftly accumulating literature, and one gets the impression that the most enthusiastic proponents of this favored belief have clung to their cherished conclusions despite the many problems inherent in the collected information (*Rotkin* 1976). There is no room here to discuss the state of the art, not only with respect to HSV2, but also in relation to the association of other viruses and cancers. Comparisons of populations with highest and lowest frequencies of cervical cancer in Colombia and Israel, both assayed similarly for antibodies to HSV2, have shown equivalent percentages of positive responses to the virus, with very little or no differences in response between cervical cancer patients and controls. The subject is extremely complicated and the reader is referred to several current reviews (*Melnick* and *Adam* 1978; *Rawls* et al. 1977, 1976; *Thiry* 1976). The statement by *Rawls* et al. (1976) that, "it is not possible at this time to conclude that HSV2 is etiologically related to cervical cancer; especially since the role of EB virus in the genesis of Burkitt's lymphoma and nasopharyngeal carcinoma still remains in doubt," is an observation with which I agree.

A major difficulty of many viral studies is that they attempt to find a relationship to oncogenicity by investigating tumor tissue, whereas the focus must be upon cells at risk immediately preceding transformation. All ascribed human oncogenic viruses are widely distributed, and their presence in individual cancer cells may indicate a phagocytic or metabolic affinity of abnormally replicating cells for nucleic acids or specific component nucleotides of contiguous organisms. It is possible that *many* candidate agents can transform cervical cells: herpes and other viruses, monilia, *Trichomonas,* gonococci, spirochetae, spermatazoa, even inorganic ions and chemical compounds. Or, perhaps none of these is an effective agent; the issue is far from settled.

The effect or interaction of several other external influences upon risk has not been resolved or adequately studied. These influences include the general hygienic condition of male sexual partners, as well as diet and medically administered substances such as hormones and therapeutic dosages.

The Effect of Ritual. Hochman et al. (1955), discussing cancer of the cervix in Jewish women of Israel, and later *Auster* (1965), reporting on Jewish women in general throughout the world, were not impressed with the rite of Niddah, which forbids sexual relations during the 7 days after cessation of menses, as the reason why Jewish women are not often diagnosed with cervical cancer. Both agreed that the majority of Ashkenasi Jewish women do not observe this ritual. It is probable that most Jewish women in the United States, Israel, and elsewhere were not aware of this rule, and it is doubtful that they would have observed it even if they were. The low risk attributed to Amish and Mormon women has not been associated with ritual; rather, in observance of a strict moral code, both of these populations eschew premarital and extra-

marital sexual activities. Departures from such taboos can be expected in any population, but they would be minimized where religious proscription is greatest.

Endogenous Variables. Conventional studies so far have not identified a strong genetic influence upon the risk of cervical cancer (*Brϕbeck* 1949; *Murphy* 1952; *Rotkin* 1966). Investigations of the effect of heredity upon human neoplasms generally appear to have dwindled, not only over difficulties in collecting reasonably complete and comprehensive data, but also because there has been virtually no resolution of a possible genetic transmission of specific prevalent cancers. Public death and disease records, when obtainable, are often highly unreliable. Large aggregates of cancers in any one family usually do not establish a degree of heritability of specific or generalized neoplastic disease in a population. Models derived from carefully controlled inbred laboratory animals cannot be directly applied to genetically panmicted humans who are exposed to a wide spectrum of oncogenic and carcinogenic events, some of which may be experienced in common by many members of the same family or perhaps limited to the same sex of an entire family. The genetic component of risk may be masked as an indirect effect upon other processes, with more direct application to metaplastic and/or cellular changes, and with specificity for individual cancers or classes of cancers. The possibility of a single gene difference, with modifiers, was proposed in relation to cervical cancer (*Rotkin* 1962, 1967a) and possibly may be extended generally to other cancers. A variety of other genetic effects upon the cell at risk may take place, perhaps governing the timetable of neoplastic development from early changes preceding initiation to succeeding endpoints, such as latency and cocarcinogenesis.

A genetic effect upon hormones associated with the menses might be considered if it could be demonstrated that such hormonal secretions can transform cells at risk of cervical cancer, but the preponderance of evidence in carefully controlled studies rules out the possibility that excesses or deficits of estrogens or androgens, or their relative proportions, are involved; and the hypothesis must be abandoned, at least until more convincing reports appear than are now available. A genetic effect upon the characteristics of spermatazoa deposited by the male with access to the cervix is another possibility, perhaps in relation to differences in synthesis of basic proteins such as histones and protamines, as has been claimed; and here there certainly would be a more direct relationship from the alteration of amino acids produced by specifically coded nucleotides, but this also requires demonstration. For the present, it can be said that, based on available familial studies, increased risk cannot be ascribed to any women from a family where cervical cancer exists in other members.

Psychological Stress. In reviewing the literature, *Kowal* (1955) cited eighteenth and nineteenth century physicians who were impressed by the frequency with which certain life situations tended to occur prior to the development of a neoplasm. These included reactions of despair and hopelessness, passive surrender, grief, and melancholia following encounters with disaster. Prevention of cancer would then include avoidance of anxiety-provoking professions, public life, amibition, rage, and violent grief, with cheerfulness as a prophylaxis to stop progression from early cancer to invasion. Attention today is focused upon stressful situations, anxiety reactions, feelings of hopeless-

ness, concealed hostilities, inability to discharge tensions, ego defenses, and other personality departures. However, any rationale that proposes cancer as a specialized somatization must assume that continuous and disorganized cellular division can be induced in some reasonable physiologic manner as the outcome of behavioral responses. A considerable literature exists dealing with the effect of a psychological component upon the risk of cervical cancer (*Tarlau* and *Smalheiser* 1951; *Stephenson* and *Grace* 1954; *Schmale* 1958; *Schmale* and *Iker* 1966), with a focus upon separation, depression, life stress, and personality patterns. It is doubtful that any of these earlier studies succeeded in resolving such a risk relationship. Special emphasis on depression immediately before detection of the cancer suffers from the oversight that the latent period of cervical cancer is an average of about 30 years. Even if a depression is considered as a promoting event, which has not been demonstrated, it is questionable that invasion would follow as quickly as is claimed. A recent study (*Niemi* and *Jääskeläinen* 1978) followed groups of patients with unipolar and bipolar depressions over a period of 10 years, during which only the numbers of expected cancers of all types, or fewer, were observed. Their conclusion was that the study had failed to establish an association of depression with increased cancer morbidity. Although an etiologic connection not has been demonstrated, an open mind must yield to the possibility that it may exist.

Institutionalization as a separate variable increasing or decreasing the risk of cervical cancer has not been investigated. Already described is the absence of risk in nuns, as well as the greatly increased risk of women who are detained in penal confines. Any effect directly or indirectly attributable to adolescent attendance in a private school, convent, or similar sequestered group has not yet been studied, nor has military services been studied.

Examination of the adolescent girl has been limited virtually entirely to findings of atypias in screening programs (*Kaufman* et al. 1970; *Wallace* and *Slankard* 1973; *Feldman* et al. 1976), which reported substantial numbers of moderate and severe dysplasias and even in situ lesions in young girls, thereby justifying Pap smear surveillance of all nonvirgin females. Studies of the teenage girl as a human entity who reflects and responds to the special pressures of her culture, not the least of which are those of her peers and of sexually aroused males, have not been conducted. There is no question but that adolescence is the central issue in determining increased risk of cervical cancer and in programs of prevention.

New Hypotheses. The resurgence of some old beliefs has demonstrated only that a number of outcomes can follow early beginnings of sexuality and many partners. Among these is an association of *Trichomonas vaginalis* with greatest risk, as suggested by several studies (*Naguib* et al. 1966; *Audet-Lapointe* 1971; *Harington* 1977), but rejected by another (*Slate* et al. 1960). It has also been suggested that the prostate of the male is a reservoir for HSV2, from which it is transmitted to the female, resulting in greater risk of developing both prostate and cervical cancers (*Centifanto* et al. 1972; *Feminella* and *Lattimer* 1974). Two studies have reported correlations between cervical and penile cancers (*Kurihara* and *Asano* 1956; *Martinez* 1969). Reports of this type tend to confirm the contribution of a putatively oncogenic agent to the female at risk, but that specifically identified agents are responsible for initiation of neoplasia has so far only been presumed.

A truly new hypothesis, already discussed and much too complex to be further detailed, involves the possible activity of specific proteins found in spermatazoa upon

cervical squamous metaplasia (*Singer* et al. 1976). Also recent are proposed associations of increased risk from nitrosamines (*Harington* et al. 1977) and smoking. *Winkelstein* (1977) reported a high correlation between incidence rates for cervical and lung cancers, suggesting that smoking and cervical cancer are related; *Schoenberg* (1978) responded that cervical cancer patients are also at greater risk of developing several other cancers, suggesting that certain female groups at greater risk of these cancers may be cigarette smokers, or that tobacco may have a direct effect. *Williams* and *Horms* (1977) also reported an association of cigarette and other tobacco use with cervical cancer. Since smoking is not venereally transmissible, it should be pointed out that sexually uninhibited young women most probably would smoke, and that although the systemic effect of tobacco upon all vascularized organs cannot be denied, the contribution of the male cannot be overlooked. Explanation of multiple primaries associated with cervical cancer, most of which are also squamous or transitional tissue, can be found in a selective genetic effect (*Rotkin* 1962, 1967a). *Naguib* et al. (1966) reported rates of abnormal smears and confirmed cases of cervical cancer as being significantly higher among *current* smokers, with rates of those who stopped smoking similar to those who never smoked, and with higher rates for those who started to smoke before age 20. However, they indicate the possibility of confounding variables such as personality, living patterns, and perhaps genotypes, as well as the use of alcohol and coffee, which often accompany smoking. There is also the likelihood that women with multiple sexual partners and early onset of coitus would be smokers.

Concluding Remarks. Cervical cancer is the one carcinoma that has been fully and exhaustively researched with regard to known and suspected epidemiologic variables. Key risk factors have been clearly identified and supported by many confirming studies. These direct variables, and also a number of indirect associations, are available in clinical practice and screening programs to identify women at maximal risk of developing cervical cancer. It is self-evident from available information that transference of lower socioeconomic and cultural populations into higher classes of income and education would result in decreased morbidity rates from cervical carcinoma by alteration of female life patterns, particularly of those in younger age groups.

The epidemiologic findings, however solidly established and useful in programs of prevention, have resulted in a pressing need for social decisions regarding the counseling of mothers and their daughters; educational programs directed at medical professionals and the general public; revision of cytologic screening programs to include nonvirgin women of *all* ages, with priorities for those at greatest risk; greater surveillance of female patients by physicians in general and special practice; and provisions of realistic sexual alternatives for the young males who, while exerting the heaviest sexual pressure upon young girls, are also much more heavily sexually driven during adolescent years than their female counterparts.

Etiologic and pathologic research is gaining momentum, and perhaps the day is near when the morphogenesis and natural history of cervical cancer will be so understood that programs of primary and secondary prevention will further reduce morbidity and mortality rates, which already are falling in areas where surveillance programs are in effect. Until that time, intervention in those processes which can launch carcinogenesis in the cervix is the best hope for minimizing this disease. The necessary information

is available, but even with better and earlier diagnosis it is always preferable to avoid cancer than to cure it.

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Pathogenesis of Carcinoma of the Uterine Cervix

L.G. KOSS

A. Historical Development

Population data on frequency of cancer of various organs cannot be considered reliable prior to 1950. Nevertheless, there appears to be little doubt that carcinoma of the uterine cervix has been one of the leading causes of cancer mortality among adult women for many centuries. It is, therefore, remarkable that within the last 25 years a significant reduction in the mortality from this disease has occurred in the United States and some other western countries. For 1978 the *American Cancer Society* projected for the first time that the rate of carcinoma of the endometrium will surpass the rate of carcinoma of the uterine cervix as the leading genital cancer in the United States. This striking change in the natural history of a major malignant disease is due to a number of factors. Despite some views to the contrary, cytologic screening has played a significant role in the lowered rate of invasive cervical cancer. This has been documented by careful epidemiologic study (*Cramer* 1974) and by population data from several well-defined geographic areas with effective screening programs, such as the Province of British Columbia (*Boyes* 1969; *Boyes* and *Worth* 1976), and Louisville, Kentucky (*Christopherson* and *Parker* 1969; *Christopherson* et al. 1970; *Christopherson* and *Scott* 1977). Other factors, such as the increased frequency of hysterectomies and perhaps a natural drop in the rate of this disease due to unknown causes, also may have contributed to the lowered rate of cervical cancer.

Cancer of the uterine cervix is, so far, the only known example of a disease which has been the object a successful, deliberate effort to promote detection and prevention. Perhaps more important from the point of view of biology, however, is that much has been learned about the natural history of this disease, possibly with major implications for the concepts of human cancer in general.

Historically, the first step in this direction was the understanding of the histologic classification of carcinoma of the cervix. This led to identification of the preinvasive and curable stages of the disease and, ultimately, to the application of means of detection on a large scale.

It is of major interest to the historian to read the introductory pages to the chapter on uterine cancer by *Robert Meyer* (1930) which traces the identification of cervical cancer as a disease entity. During the closing years of the nineteenth century and the first 12 years of this century, the pathogenesis, nomenclature, and clinical significance of histologic patterns were quite bewildering. Even in the monumental book by *Schottlaender* and *Kermauner,* published in 1912, the notions concerning carcinoma of the uterine cervix and endometrium were not clearly sorted out.

Within the development of histologic examinations of human tissues for purposes of disease identification and with the introduction of the biopsy for the diagnosis of uterine cancer (*Ruge* and *Veit* 1878; *Ruge* 1890), a major step forward took place in the classification of the disease. Thus, the foremost interpreter of the biopsy, *Robert Meyer,* clearly separated carcinoma of the uterine cervix from carcinoma of the corpus. Among carcinomas of the cervix, he separated "solid" carcinomas, comprising all epidermoid cancers and their keratinizing variants, from adenocarcinomas of endocervical origin. *Meyer*'s classification has been generally accepted, and it would be surprising today to many a young pathologist to learn about this extraordinarily confusing and yet relatively recent period in the pathology of genital cancer.

An understanding of the sequence of morphological events in the genesis of epidermoid carcinoma was greatly enhanced by *Schauenstein,* who, in 1908, published a paper on atypical surface epithelium of the cervix. He clearly identified the surface changes as histologically identical to those observed in invasive cervical cancer and suggested that the abnormal surface epithelium was the source of invasive cancer. *Schauenstein* was by no means the first observer to record such findings. Similar illustrations were published by prior observers, such as *Amann* (1897), *Cullen* (1900), and many others. Yet the formulation of the principle of origin of cervical cancer from precancerous epithelium appears to belong to *Schauenstein.* The term "carcinoma in situ" in reference to surface changes was clearly introduced by *Schottlaender* and *Kermauner* in 1912 but was subsequently popularized by *Broders* (1932).

A number of other observers confirmed *Schauenstein*'s observations: *Pronai* (1909) and *Rubin* (1910), and in later years, *Schiller* (1927, 1928). While these initial observers had little doubt about the biologic significance of the observed surface abnormalities and considered them as manifestations of cervical cancer, a major follow-up study of 18 patients by *Scipiades* and *Stevens* (1938) disturbed this facile thinking. Three of these patients received no treatment; two of them ultimately developed invasive cancer of the cervix, but one remained free of disease. This report led the great cancer pathologist, *James Ewing* (1940), to the conclusion, "It thus appears that while some of the lesions must progress and become true cancer, others may be reversible and undergo spontaneous regression, so that a positive diagnosis of cancer may not be given."

In a nutshell, Ewing's statement opened the door to the controversy which at the time of this writing (1979) has not yet come to rest. The problem became still more acute with the introduction of cytologic mass screening (*Papanicolaou* and *Traut* 1943), which brought to light an unexpectedly large number of intraepithelial abnormalities of uncertain prognosis in well women and ushered in the era of "the great debate" on precancerous lesions of the uterine cervix.

It is the purpose of this contribution to examine critically the known facts in this controversy and to present a biologic concept of precancerous epithelial lesions in man which differs from the classical notions about invasive human cancer.

B. Epidemiology

Although an extensive discussion of the epidemiology of carcinoma of the uterine cervix will be found elsewhere in this book, a brief summary is essential for the clear presentation of data on the pathogenesis of this disease.

In 1842 an Italian physician, *Ringoni-Stern,* published a series of charts based on mortality statistics from the death register of the city of Verona for the years 1760–1830. This unsung and obscure pioneer of cancer epidemiology was presumably the first to point out that "cancer of the uterus" was encountered with much greater frequency in married women and widows than in unmarried women and nuns. The age distribution in *Ringoni-Stern*'s statistics, showing that "uterine cancer" occurred first in women between 30 and 40 years of age and that it reached its peak in women between 40 and 60 years of age, would strongly suggest that he was dealing primarily

with the epidermoid cancer of the uterine cervix and that he thus introduced the concept of sexual events into the epidemiology of cervical cancer (*Koss* 1974).

Considerable evidence has accumulated that epidermoid cancer of the uterine cervix and related precancerous states are associated with the following risk factors.

1. Onset of sexual activity before the age of 20
2. Multiple sexual partners (promiscuity)
3. Multiple pregnancies
4. Young age at birth of first child
5. Low social and economic status
6. Poor sexual hygiene
7. Low educational level
8. Promiscuous male partner(s)

Nearly all of these factors have been confirmed in multiple studies (*Rotkin* 1973; *Miller* 1978; *Pauli* 1978; *Sachs* 1978). The promiscuity of male partners was first observed as an important factor by *Pridan* and *Lilienfeld* (1971) in a study of Israeli women. In a recent study of very young, promiscuous girls ages 12–15 by *Hein* et al. (1977), it was observed that a relatively short period of sexual exposure (12–48 months) could trigger precancerous events at the cellular level in over 3% of such girls. The biologic significance of these changes will be discussed later.

The epidemiologic data point out that epidermoid cancer of the uterine cervix appears to behave similarly to a venereal disease. This has led to the search for a possible transmissible trigger factor. The current primary target of these investigations is herpes virus type II (*Kessler* 1974; *Miller* 1978). The evidence is based on serologic data and on the demonstrated presence of viral proteins in cells of cervical cancer by fluorescence (*Aurelian* et al. 1973). Another possible viral agent is wart virus (*zur Hausen* 1976), the causative factor in condylomata acuminata. The relationship of condylomata acuminata to precancerous lesions of the uterine cervix is a focus of current interest (*Purola* and *Savia* 1977; *Meisels* and *Fortin* 1976; *Meisels* et al. 1977; *Laverty* et al. 1978; *Morin* and *Meisels* 1980).

The possibility that spermatozoa may act as transmissible agents by entering epithelial cells and modifying their genome, a theory first advocated by *Coppleson* and *Reid* (1968), has recently received major support from experimental studies. It has been shown that spermatozoa may indeed transform the genome and biochemical activity of cells in culture (*Bendich* et al. 1976).

Regardless of the attractiveness of these considerations, the direct biologic cause of cervical cancer must still be considered unknown, as is the case with human cancer in general. It appears most likely that the sequence of cellular events leading to invasive epidermoid carcinoma of the cervix may be triggered by numerous factors, and that this sequence is much more complex than has been shown by epidemiologic studies.

Virtually nothing is known about the epidemiology of the relatively uncommon endocervical adenocarcinoma.

C. Sequence of Morphological Events

I. Epidermoid Carcinoma

Considerable information is available on the site of origin and on events at cellular and tissue levels in the pathogenesis of epidermoid carcinoma.

1. Anatomic Events

a) Transformation Zone

Hinselmann (1933), the father of colposcopy, must be credited with the origin of the concept that the early stages of development of epidermoid carcinoma are not visible to the naked eye but may be observed on careful inspection of the cervix with a magnifying instrument, the colposcope. The acceptance of colposcopy as an essential step in the evaluation of the uterine cervix (but not as a means of primary cancer diagnosis, as originally advocated) has significantly contributed to our understanding of the sequence of events in carcinogenesis. It has been shown that in 90% of all patients the initial developments take place in a relatively small area of squamous epithelium abutting on endocervical epithelium (*Kolstad* and *Stafl* 1977). This area, usually adjacent to the external os of the cervix, has been given the name transformation zone (Fig. 1).

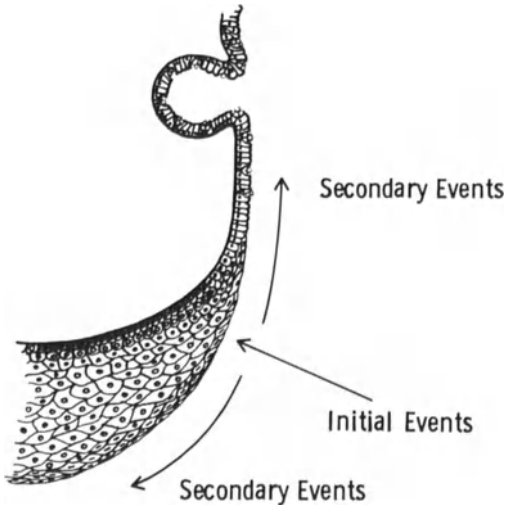


Fig. 1. Diagrammatic illustrations of cancerous events in the epithelium of the uterine cervix. The initial events usually take place in the squamous epithelium of the squamocolumnar junction or the so-called transformation zone. The direction of the secondary events will result in lesions of different configuration. Lesions spreading to the endocervical canal will be generally made up of small, poorly differentiated cells (see Figs. 5 and 9). Lesions located on the squamous epithelium of the portio tend to form keratin (see Figs. 6 and 10). From *Koss* (1979)

The reasons why the transformation zone is the primary target of cancerogenic events have not been determined with complete certainty. It has been shown that this area of the cervical epithelium contains more cells in premitotic or mitotic phases of the cell cycle. Such cells are perhaps more susceptible to cancerous transformation than quiescent epithelial cells.

The colposcopic identification of abnormal events within the transformation zone is based mainly on patterns of vascular changes that accompany cancerous events. Why such changes take place is not known. A colposcopic examination of the cervix is extremely helpful in outlining the size and precise location of precancerous events discovered by cytology.

From the transformation zone cancerous developments may spread either to the endocervical canal or to the epithelium of the portio, or in both directions (Fig. 1). The mechanism of this spread is unknown, although two possibilities must be considered: Either the neoplastic cells replace the benign epithelium, or the neoplastic process spreads by progressive transformation of the cells in the adjacent epithelium.

The histologic patterns of the lesions depend greatly on the direction of the anatomic spread: lesions extending to the endocervical canal tend to be composed of poorly differentiated cells, whereas lesions extending into the portio tend to form keratin. The reasons for the morphological adaptation of the cancerous process to the preexisting epithelial pattern are unknown. It may be that some of the normal differentiation mechanisms are preserved in the epithelium during the intraepithelial stages of the cancerous process.

b) Endocervical Canal

Some precancerous lesions of the epidermoid type originate directly in the endocervical canal. These lesions tend to be composed of small cancer cells which may produce mucus. The question as to the precise cell of origin of these lesions is unimportant, but it is generally assumed that such lesions are progeny of basal or reserve cells of the endocervical epithelium.

2. Early Cellular Events

Repeated population screening for cancer of the uterine cervix has clearly shown that the initial morphological cancerous development observed in previously normal women is the so-called superficial and intermediate squamous cell dyskaryosis. This term was suggested by *Papanicolaou* in 1949 to describe mature squamous cells with morphologically normal cytoplasm but with nuclear abnormalities. The latter vary from enlargement and multiplication to marked hyperchromasia. Perinuclear vacuoles are frequently noted in such cells, a phenomenon named "koilocytotic atypia" some years ago (*Koss* and *Durfee* 1956).

Within recent years it has been suggested that at least some of the koilocytotic cells are derived from modified (flat) condylomata acuminata (*Purola* and *Savia* 1977; *Meisels* and *Fortin* 1976; *Meisels* et al. 1977). Electron microscopic documentation of

the presence of wart virus particles in the nuclei of such cells has been published (*Morin* and *Meisels* 1980). This evidence casts an interesting light on the possible role of wart virus in the genesis of dyskaryotic cells, and hence on the early stages of genesis of cervical cancer, particularly in view of the known persistence of such changes over a period of many years and their association with more advanced neoplastic intraepithelial abnormalities (*Koss* et al. 1963; *Purola* and *Savia* 1977).

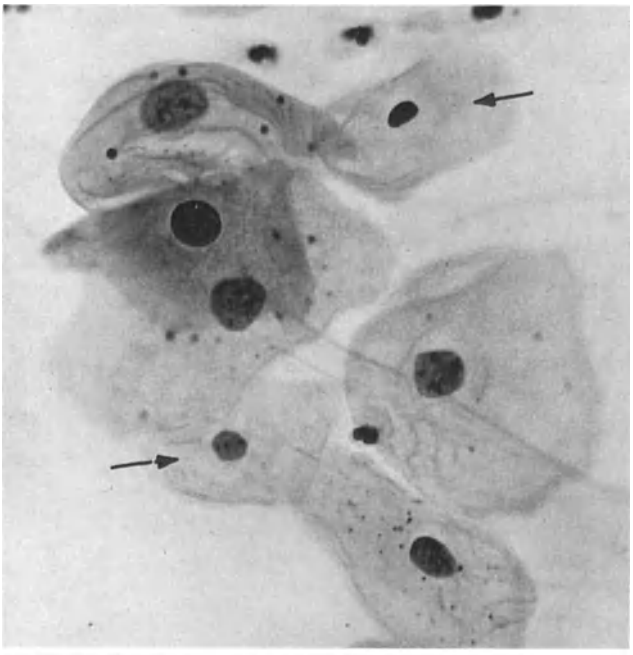
It is of interest that if observed in women in the childbearing age, the cytoplasm of the dyskaryotic squamous cells appears to be responsive to the hormonal cyclic changes. In this respect the dyskaryotic cells are in unison with normal squamous cells and follow the hormonal pattern of the smears, as described elsewhere (*Koss* 1979). A few points of differential diagnosis must be mentioned. Folic acid deficiency and radiotherapy may also lead to nuclear enlargement. Changes similar to dyskaryosis may be induced by certain alkylating chemotherapeutic agents and may also be observed in immunosuppressed patients, such as recipients of renal allografts. However, the behavior of such changes in the latter two groups of patients appears to be similar to the spontaneously occurring abnormalities (*Koss* 1979).

Biopsies of the cervical epithelium corresponding to such cellular developments usually show a rather well-organized squamous epithelium with nuclear abnormalities, in addition to excessive and sometimes abnormal mitotic activity at all epithelial levels. The lesion is usually identified as mild dysplasia, borderline lesion, or cervical intraepithelial neoplasia, grade I, and is generally considered of limited clinical significance (Fig. 2).

It behooves us to reflect briefly on the biologic meaning of these events. It must be assumed that the nuclear changes represent a clone, or clones, or cells that have undergone a major transformation. Such cells have an abnormal DNA content (*Wagner* et al. 1972) and often an abnormal complement of chromosomes (*Spriggs* et al. 1971; *Granberg* 1971). The level of mitotic activity accompanying such cell changes clearly suggests that the epithelial cells are mutliplying with a frequency much higher than the normal epithelium (*Rubio* and *Lagerlöf* 1974). The changes, therefore, represent the formation of a clone of cells that have an advantage over normal cells and represent a family of "fitter cells," a concept formulated by *Cairns* (1975) to explain the events in epithelial carcinogenesis. The relatively modest morphological changes at the cell and tissue level must, therefore, reflect a major biologic upheaval within the target epithelium. The clinical significance of these changes will be discussed subsequently.

3. Outcome of Early Cellular Events

The outcome of early cellular events is difficult to predict. There is excellent evidence that not all patients with the cellular changes described above will necessarily develop identifiable precancerous lesions or clinical cancer. *Richart* and *Barron* (1969) have calculated that only about 60% of the untreated and untouched early lesions (mild dysplasia) will progress to carcinoma in situ within 10 years. It may well be that 60% is a high estimate because the patients selected for this prospective study had three consecutive abnormal smears. *Nasiell* et al. (1976) estimate that only about one-third of these abnormalities will either persist or progress, which may be a more realistic appraisal. It is evident that two important questions must be raised: (1) Are the pa-



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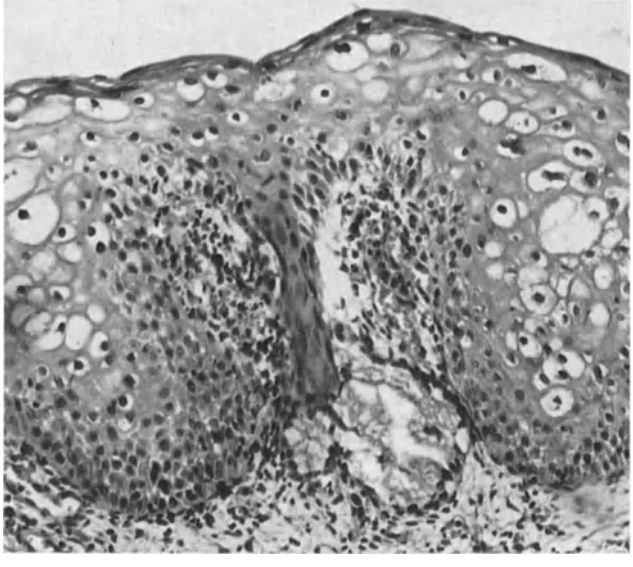

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Fig. 2a, b. Initial cellular events in carcinogenesis of the uterine cervix observed in a 17-year-old, sexually active girl. **a** Cervical smear. Dyskaryosis of superficial squamous cells. There is obvious nuclear enlargement and increased hyperchromasia in several of the large cells. This must be compared with normal nuclei also seen in the same field *(arrows)*. It must be noted that the cytoplasm of the dyskaryotic cells is transparent, delicate, and, in the top cell, folded, thus indicating a hormonal response. × 560. **b** Biopsy of the squamous epithelium of the transformation zone. The epithelium is orderly, but large cells with clear cytoplasm and enlarged single or multiple nuclei may be observed throughout. The term koilocytotic atypia has sometimes been applied to such lesions. The lesion is a flat form of a condyloma acuminatum. The lesion disappeared after the biopsy and the young patient remained free of disease for a period of 3 years of follow-up. × 350

tients with disappearing early lesions "cured"? (2) What are the biologic mechanisms responsible for the unpredictable behavior of early cancerous changes?

The prevailing theory of experimental epithelial cancerogenesis assumes that two events must take place for a cancerous clone of cells to appear: the initiation and the promotion (*Berenblum* 1974). It is known that if a potent carcinogen is applied to target epithelium and then withheld, a regression of the lesions, such as squamous papillomas, may take place. If the carcinogen is reapplied after a suitable time interval, the lesions will reappear on short notice. This sequence of events, illustrated in Fig. 3, suggests that the process of initiation is irreversible, but that its morphological expression may disappear.

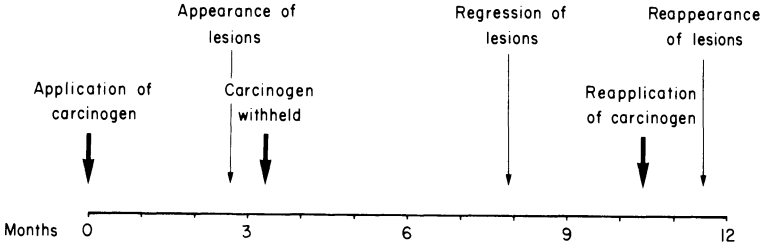


Fig. 3. Diagrammatic representation of events in experimental epithelial neoplasia, for example, following application of tar to the skin of a rabbit's ear. If the carcinogen is withheld, the lesions disappear, but if the carcinogen is reapplied, the lesions promptly reappear

It is possible that similar sequences of events may occur within the epithelium of the cervix. The morphological expression of cancerous events may disappear but the basic changes in the target epithelium remain. Thus, women with "disappearing" lesions presumably remain at risk. Supporting evidence for this concept is fragmentary but available nevertheless. In personal follow-up studies (*Koss* et al. 1963) it was noted that a temporary reversal to normal epithelium may occur after biopsies of precancerous lesions of the uterine cervix, followed by a return of the abnormal epithelium. In the same study it was repeatedly recorded that abnormal cervical smear patterns may return to normal, only to show abnormal cells again after a few months or even years of morphological normalcy. Epidemiologic follow-up studies have also yielded data showing that there is a major risk of subsequent cancerous development in women with early cancerous changes. *Stern* and *Neely*'s data (1963) suggest that the risk factor is 1600 times, and *Nasiell* et al. (1976) calculated it to be 2000 times above normal.

It is much more difficult to respond to the question on the nature of biologic mechanisms responsible for the unpredictable behavior of early precancerous epithelial lesions. If, in fact, an external transmissible carcinogen acts on cervical epithelium, then, according to the experimental scheme, withholding of the carcinogen may lead to a return to morphological normalcy. An experimental setting in which women with precancerous lesions are be enjoined from engaging in sexual intercourse is impossible to create in our free society. Thus, the theory will presumably remain anecdotal. In fact, I have observed on several occasions that an abnormal smear pattern in young women

led to a decrease in sexual activity followed by a disappearance of the abnormalities. The cause-effect relationship of such events is obviously impossible to prove. Unfortunately, experimental cancerogenesis of the cervix sheds little light on the human model, and the gathering of data on a large group of reformed prostitutes would surely offend civil libertarians. Data on disappearing lesions culled from the literature are contradictory. In tables published by *Nasiell* et al. (1976), the rate of disappearing "moderate dysplasias" was somewhat higher in postmenopausal women than in younger age groups. However, in *Kinlen* and *Sprigg*'s study (1978), regression of abnormalities occurred mainly in women below the age of 40. Thus, the clinical events leading to regression of precancerous developments remain unknown.

There remains the possibility that spontaneous DNA repair mechanisms may occur in the affected epithelium. Such options were discussed by *Cairns* (1975). It may also be postulated that immunologic rejection mechanisms of as yet unknown nature may be operating in the affected epithelium. It can be argued that the appearance of epithelial abnormalities in immunosuppressed patients favors an immunologic mechanism of rejection, but the hard data are clearly not available.

4. Late Cellular Events

The study of cytologic abnormalities that follow the early cellular events described and discussed above shows the occurrence of new abnormal cell populations characterized largely by major nuclear and cytoplasmic abnormalities. A schematic representation of the nuclear events is shown in Fig. 4. The nuclei become enlarged and of unequal size. The chromatin forms coarse granules which accept nuclear stains more intensely, leading to hyperchromasia. Large nucleoli may be observed. The configura-

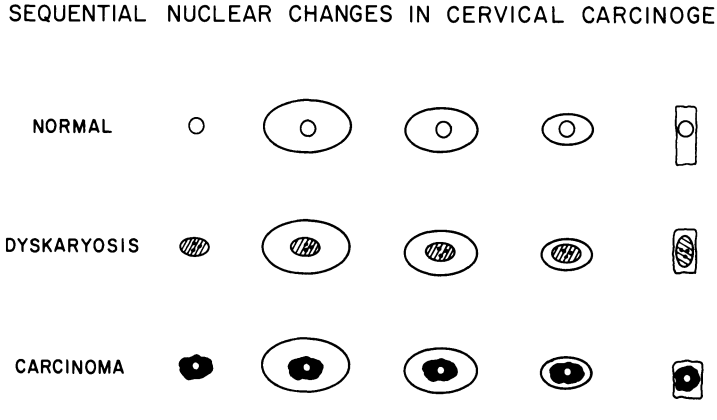


Fig. 4. Diagrammatic representation of early and late cellular events in the genesis of carcinoma of the uterine cervix. Sequential changes in the morphology of the nuclei are shown vertically in the *left row.* Changes in squamous cells of various sizes *(three center rows)* and in the endocervical cells *(right row)* are also shown. Increased nuclear hyperchromasia, irregularity of nuclear outline, and the appearance of prominent nucleoli in carcinoma are stressed.

tion of the cytoplasm may vary remarkably, and cells of odd sizes and shapes may appear. The ratio of the volume of nuclear material to the volume of cytoplasm (the nuclear:cytoplasmic ratio) is often changed in favor of the nucleus. Abnormal mitotic activity is often noted.

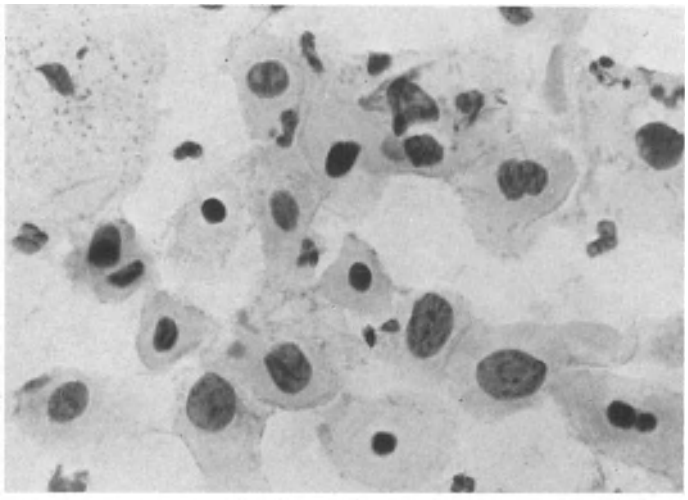
The nuclear abnormalities correspond to abnormal DNA patterns (*Sandritter* 1964) and to abnormal numbers of chromosomes (*Granberg* 1971; *Sandberg* and *Hossfeld* 1974). However, there is still considerable debate whether these quantitative changes in the amount of DNA account for all the nuclear changes. It may be pointed out that tetraploid and even octaploid cells found in normal tissues do not necessarily display hyperchromasia. Thus, the possibility that the packaging of DNA is altered in cancer cells must be considered (*Koss* 1979).

Cytoplasmic abnormalities vary according to the anatomic spread of the lesions (Fig. 1). Cells from lesions extending primarily into the squamous epithelium of the vaginal portio tend to have abundant cytoplasm, sometimes of the keratinizing variety. In such cells the nuclear:cytoplasmic ratio is not necessarily significantly altered (Fig. 5).

Cells from lesions extending primarily into the endocervical canal tend to be smaller and are characterized by cyanophilic (basophilic) cytoplasm, which may be quite scanty in relation to the nuclear size. Sometimes such cells show cytoplasmic vacuoles which contain mucus (Fig. 6).

Biopsies from the affected epithelium show a degree of epithelial upheaval which is significantly greater than in the early lesions shown in Fig. 2. The visual perception of the degree of abnormality will vary, again according to the anatomic location of the lesions. Lesions affecting the squamous epithelium of the portio often appear more orderly and are made up of larger squamous cells which may even form keratin on the epithelial surface (Fig. 5). Lesions affecting the endocervical canal appear less differentiated and are composed of small, more classically cancerous cells (Fig. 6). Some of the differences in the nomenclature of this group of lesions, to be discussed in Sect. D of this chapter, have to do with the anatomic location of the lesions and not necessarily with their biologic potential. In any event, the term "carcinoma in situ" is appropriately applied to those lesions which closely resemble invasive carcinoma of the cervix. It must be remembered in this context that the histologic patterns of fully invasive carcinoma may vary enormously as to size of the component cells and degree of differentiation (keratinization). Hence, it is unrealistic to confine the term "carcinoma in situ" to lesions composed of only small cancer cells (*Koss* 1979).

The morphological evidence, briefly summarized above, clearly indicates that with the progression of the cancerous process, new clones of cells have emerged in the affected epithelium. Whether these new clones are still "fitter" than the clones of the earlier changes is a matter for debate. In any event, profound rearrangements of the genome of the cells have taken place. It has not been resolved whether abnormalities of DNA quantitated by cytophotometric measurements of Feulgen stain or the assessment of chromosomal complement, cited above, are the cause or the effect of the fundamental changes occurring during carcinogenesis. The possibility that the truly significant changes are much more subtle and affect primarily the mechanisms of cell division has not been studied for lack of research tools and approaches. However, cellular morphology is a convenient and remarkably accurate mirror of cancerous transformation in the epithelium of the uterine cervix.



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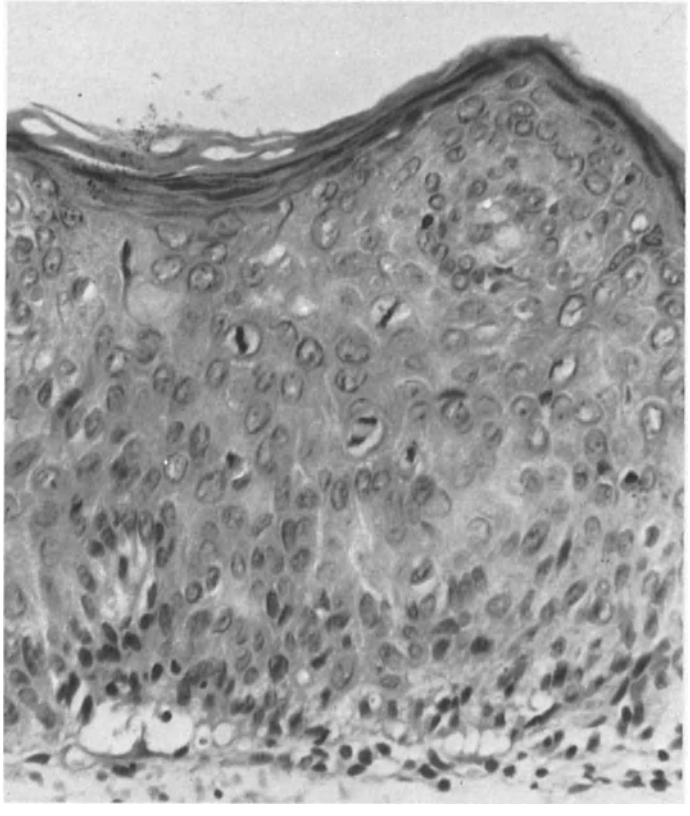

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Fig. 5a, b. Late cellular events in the genesis of epidermoid carcinoma of the uterine cervix involving squamous epithelium. **a** Cervical smear. Squamous cancer cells of varying size are characterized by enlarged and coarsely granular nuclei. In this type of disease the cytoplasm often remains abundant and shows formation of keratin. × 560. **b** Biopsy of squamous carcinoma in situ (CIN grade III) of uterine cervix, corresponding to the smear. The epithelium may appear orderly but is in reality composed of highly abnormal, large, well-differentiated squamous cancer cells shown in **a**. Note also intense mitotic activity and, in this example, keratin formation on the epithelial surface. × 350

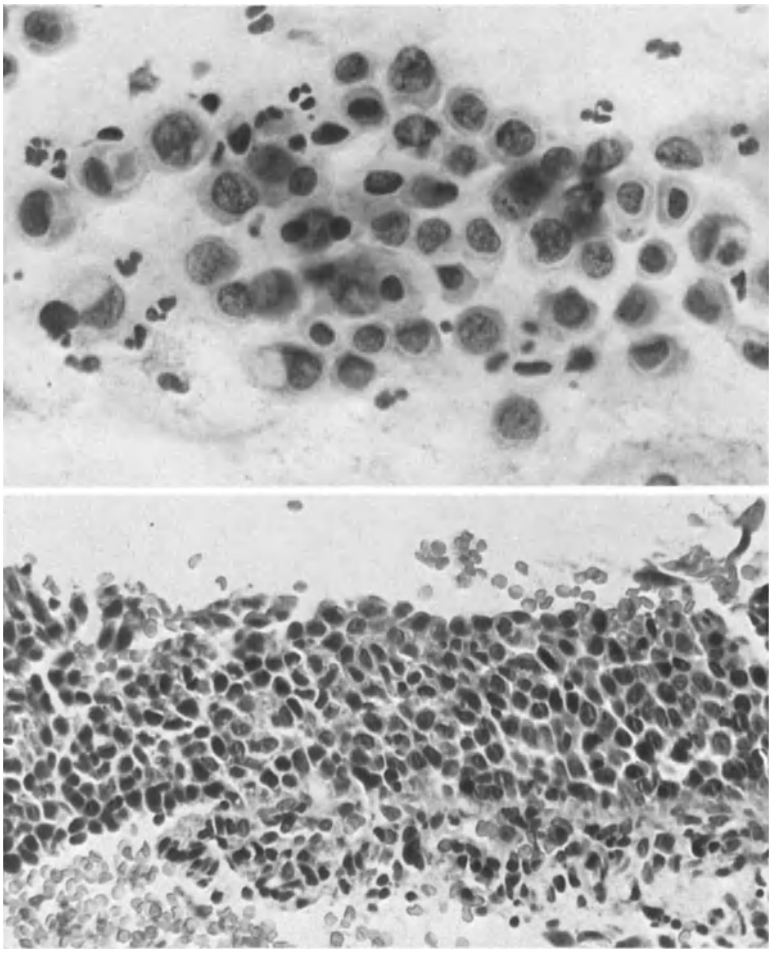

Fig. 6a, b. Late cellular events in the genesis of epidermoid carcinoma of the uterine cervix involving endocervical canal. **a** Generally small cancer cells with large, coarsely granular, hyperchromatic nuclei. Note the presence of cytoplasmic vacuoles in some of the cells, suggestive of their origin in the mucus-secreting endocervical epithelium. × 560. **b** Biopsy fragment of epidermoid carcinoma in situ (CIN grade III) involving endocervical canal. Compare the generally much smaller size of cancer cells in this figure with the large cancer cells of keratinizing type shown in Fig. 5. × 350

5. Outcome of Late Cellular Events

An understanding of precancerous events in man would be much simpler if follow-up studies of the late cellular changes invariably led to invasive carcinoma of the cervix, perhaps after a suitable interval of several years. Unfortunately for the science and fortunately for the patient, this is most emphatically not the case. In fact, those few studies where precancerous lesions of the cervix, regardless of morphology, were fol-

lowed without treatment under reasonably uniform conditions of observation (*Koss* et al. 1963), the behavior of all intraepithelial lesions was remarkably similar, regardless of morphologic configuration. While the probability of regression is reduced with the increasing severity of the epithelial change, this may conceivably be due not only to biologic behavior patterns, but also to the larger size and protected site of the histologically more advanced lesions, which commonly are located within the endocervical canal. While invasive carcinomas may and do develop from the intraepithelial lesions, this development is not necessarily related to morphological degree of abnormality, as is discussed in Sect. D of this chapter.

6. Onset of Invasive Carcinoma

Regardless of the unpredictable behavior of intraepithelial neoplastic lesions, a certain percentage of these lesions, probably not exceeding 20%–25%, will ultimately progress to invasive carcinoma. Little is known beyond broad statistical data on the time required for the intraepithelial lesion to invade. The age differences between women with intraepithelial lesions and women with invasive carcinoma may vary from 10 to 20 years, depending on the populations studied and the morphological definitions. Thus, it may be assumed that the process for most women takes many years, but there remain the personally observed and well-documented cases wherein only 1 or 2 years elapsed from the discovery of the intraepithelial lesions until the onset of invasion, sometimes in spite of attempts at local treatment.

Although it has been claimed (*Ng* and *Reagan* 1969) that early invasive cancer (microinvasive carcinoma) is associated with characteristic morphological cell changes, this is not necessarily the case in my experience. It must be assumed, however, that the process of invasion is associated with some important modifications either in the cells comprising the intraepithelial lesion or in the protective mechanism which normally prevents invasion. Cell changes, such as the emergence of a particularly aggressive cell clone or a cell clone producing a proteolytic enzyme sufficient to weaken the basement lamina and the underlying collagen, may be considered as likely, though unproven, events. Little thought has been given to the possibility that the quality of the connective tissue barrier may be modified, although changes in the agglutinability of fibroblasts by lectins have been reported in intraepithelial neoplasia by Koprowska's laboratory (*Chaudhuri* et al. 1975).

The onset of invasion also signals another important biologic event: irreversibility of the cancerous process. Here again, we lack hard scientific data to identify the factor or factors responsible. Is the property of irreversibility vested in the tumor or in the host? Is it a local phenomenon or, as is fashionably thought today, an immunologic defect? We simply lack the information to answer these questions, although speculative considerations could easily fill many pages.

II. Adenocarcinoma

Adenocarcinoma comprises only about 5%–10% of cervical cancers. Information pertaining to the sequence of events in the development of cervical adenocarcinoma is only fragmentary.

1. Early Cellular Events

Well-formed columnar endocervical cells may show evidence of dyskaryosis, as defined for the squamous cells on the preceding pages. In such cells the normal mucus production is retained, while nuclear enlargement and the presence of nucleoli may be noted (Fig. 7). Unfortunately, such changes do not have the same specificity as the changes

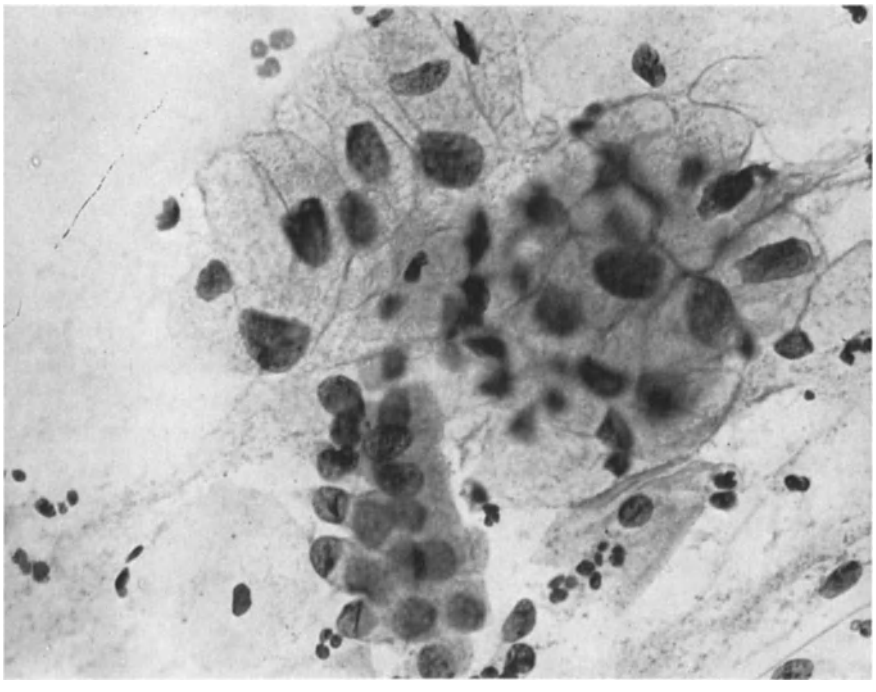

Fig. 7. Endocervical cell dyskaryosis, cervical smear. Note the large, columnar, mucus-producing cells of endocervical type with abnormally large, hyperchromatic nuclei. In the *bottom part* of the photograph a cluster of normal endocervical cells may be seen. × 560

in squamous cells. Similar abnormalities of endocervical cells may also be caused by inflammatory or regenerative events, or even by progesterone-containing contraceptive hormones. Because of the lack of specificity of the early cellular abnormalities, no information is available on the probability of development of subsequent endocervical

adenocarcinoma in such patients. Nonetheless, it has been repeatedly shown (*Koss* 1979; *Boddington* et al. 1976) that progression of such changes to endocervical adenocarcinoma may in fact occur, often after many years of follow-up. The review of prior smears on a group of patients who subsequently developed endocervical adenocarcinoma revealed six patients with cellular abnormalities occurring from 24 to 95 months prior to the onset of clinical disease (*Boddington* et al. 1976).

It must be mentioned that in some patients endocervical cell dyskaryosis will lead to the formation of epidermoid carcinoma, and not of adenocarcinoma. The epidermoid lesion is usually made up of small, undifferentiated cells, sometimes showing focal formation of glands and mucus. Some obervers class such lesions as mucoepidermoid carcinoma (*Hamperl* and *Hellweg* 1957). Thus, the tendency of the normal endocervical epithelium to undergo squamous metaplasia may also manifest itself in cancerous transformation. Some endocervical adenocarcinomas are heralded not by changes in endocervical cells, but by abnormalities in squamous cells. In some of these patients simultaneous and coexisting lesions of the epidermoid and glandular type may be observed, suggesting that common biologic denominators may be operative in cancer of the uterine cervix regardless of the histologic pattern of the lesions (*Lauchlan* and *Penner* 1967; *Koss* 1979).

2. Late Cellular Events

The existence of adenocarcinoma in situ has been repeatedly recorded (*Friedell* and *McKay* 1953; *Koss* 1979). The lesion is defined as the presence of cancerous changes within endocervical glands in the absence of stromal invasion. However, the latter is difficult to identify because of the extreme patient-to-patient variability in the anatomic distribution of endocervical glands. Thus, what may be invasive cancer in one patient is in situ in another. The matter is complicated even more by the fact that some forms of endocervical adenocarcinoma, the so-called adenoma malignum (*McKelvey* and *Goodlin* 1963), are very well differentiated and may retain the deceptively benign appearance of the component glands, even in deeply invasive and metastatic foci. Nevertheless, *Büttner* and *Kyank* (1973) observed the progression of carcinoma in situ of the endocervical type to invasive carcinoma within 11 years.

The cells of endocervical carcinoma in situ may still retain the columnar configuration of the endocervical cells of origin, but the nuclear changes are more marked than in endocervical cell dyskaryosis. Furthermore, some obviously malignant glandular cells are usually present, often in sheets (*Koss* 1979; *Krumins* et al. 1977).

The transition from endocervical adenocarcinoma in situ to invasive carcinoma is not nearly as clearly defined as for epidermoid cancers, either in the cytologic sample or in the tissue. The cells show the characteristic configuration of adenocarcinoma: large, sometimes hyperchromatic nuclei with coarsely granular chromatin and large, irregularly shaped nucleoli. The cytoplasm may vary in configuration from columnar to round and in amount from abundant to scanty. Similarly, the histologic patterns of the tumor may vary from adenoma malignum to poorly differentiated adenocarcinoma (Fig. 8). Microinvasive adenocarcinoma has not been clearly defined, although a few possible examples were shown by *Qizilbash* (1975) and by *Krumins* et al. (1977).

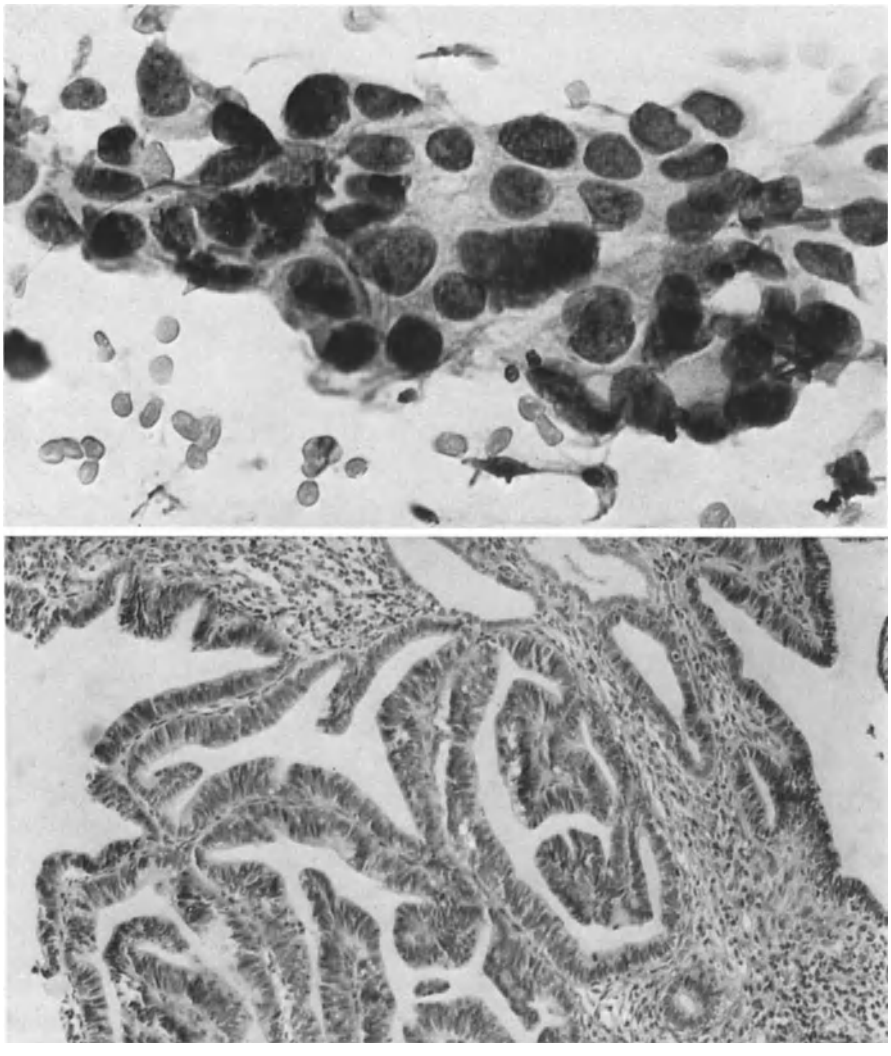

Fig. 8a, b. Endocervical adenocarcinoma. **a** Smear showing a cluster of cancer cells with highly abnormal, coarsely granular, hyperchromatic nuclei. Specific cytoplasmic features cannot be seen in this photograph, but this manner of cancer cell clustering is often observed in papillary adenocarcinomas. × 560. **b** Biopsy of invasive endocervical adenocarcinoma. Papillary arrangement of the cancerous epithelium may be noted. × 150

III. Biologic Interpretation of Morphological Events

As may be seen from the preceding brief summary, the sequence of cellular events is much better known and understood in the cancerogenesis of epidermoid carcinoma than adenocarcinoma of the uterine cervix. There are two principal reasons for this:

the anatomic location of the endocervical glands and the limited ability to sample them repeatedly, as well as the relative rarity of endocervical adenocarcinoma.

Nevertheless, there are certain similarities between the two variants of cervical cancer. The occurrence of carcinomas, whether in situ or invasive, is preceded by a sequence of events at the cellular level. The first observable morphological events pertain to relatively modest nuclear abnormalities occurring within cells that have retained most, if not all, of their cytoplasmic functions: cyclic hormonal response in the squamous cells and mucus formation in the endocervical cells. It is only with progression of the cancerous process and increasing degree of nuclear abnormalities that the cytoplasm becomes abnormal and loses its primary inherited functional characteristics.

It would appear, therefore, that those functions of the cell genome which provide for cytoplasmic differentiation are affected late in the course of carcinogenesis in the uterine cervix, whereas the functions pertaining to cell multiplication are affected early and are presumably the first important carcinogenic event which may lead directly to invasive cancer.

The emergence of a clone, or clones, of morphologically highly abnormal, clearly identifiable cancer cells, is not an essential prerequisite for invasive cancer. Nevertheless, it is a common, though biologically late, occurrence, presumably based on rearrangement of the cellular DNA affecting cytoplasmic differentiation. One can postulate that DNA instability, triggered by a carcinogenic agent, or agents, spreads from one segment of the DNA genome to another affecting DNA functions in order of susceptibility to injury. Apparently, the apparatus governing the mechanism of cell multiplication is most readily affected, whereas the apparatus for cytoplasmic differentiation is more resistant to change. The matter may be still more complex because further transformation of malignant cells may trigger the emergence of metabolic codes that are normally suppressed, resulting in the appearance of cytoplasmic functions that normally belong to other cell systems, such as the production of polypeptide hormones. This event is rare in cervical cancer (*Jones* et al. 1976), but it has been observed with considerable frequency in tumors mainly of foregut origin, such as lung cancer (*Lipsett* et al. 1964). To the best of my knowledge, the appearance of the suppressed cytoplasmic functions has never been observed in carcinoma in situ and must be considered a late event occurring in invasive cancer only. The diagram illustrating the possible correlation of morphologically and biologic events in cervical cancer is shown in Table 1.

Table 1. Possible correlation of biologic and morphologically events in carcinogenesis of the uterine cervix

Sequence of changes	Cell genome$_{max}$	Cell morphology
1.	Deregulation of mitotic activity	Dyskaryosis
2.	Deregulation of cytoplasmic differentiation a) Moderate b) Marked	Morphological cancer Intraepithelial Invasive
3.	Release of suppressed cytoplasmic functions	Cancer (invasive)

D. Clinical Significance of Morphological Patterns – Concept of Intraepithelial Neoplasia

I. Natural History of Precancerous Intraepithelial Lesions

The study of histologic patterns of invasive cancer and their correlation with clinical events has established the pathologist's ability to predict and prognosticate the course of disease. In fact, the correlation of histologic patterns of fully developed cancer with clinical course is generally accurate and reliable, whether the cancerous process is of epithelial or nonepithelial origin.

Population screening for cancer of the uterine cervix has brought to light a number of facts about precancerous intraepithelial changes that are at significant variance with this concept. The prevalence of intraepithelial changes established by screening within a given population is invariably much higher than the rate for invasive cancer. This could be explained by the presence of accumulated lesions of varying ages, simultaneously discovered. More importantly, however, the true incidence of new lesions in a previously screened "clean" population was also much higher than the rate of invasive cancers that could be expected to develop in this population at a later date. For example, in a study of women, patients of Planned Parenthood in New York City, the incidence of early precancerous changes developing after elimination of prevalent lesions in three consecutive screenings remained constant at approximately 6/1000 (Table 2, and *Koss* 1969). Similar observations on a constant and similar rate of "dysplasia" in previously screened women were reported by *Christopherson* (1969). This

Table 2. Cytologic screening for cervix cancer of Planned Parenthood participants in New York City 1965–1968. In parentheses the number of women screened

Sequential screens	Initial cellular events	Advanced cellular events	Invasive cancer
1 (37 420)	12.7/1000	10.2/1000	0.5/1000
2 (11 243)	8.5/1000	4.5/1000	0
3 (3 063)	6.5/1000	3.2/1000	0
4 (144)	6.0/1000	0	0

must be compared with the rate of invasive carcinoma of the cervix for a comparable population. The age-adjusted incidence rate of invasive cervical cancer reported from British Columbia for 1955, before the effects of screening could be observed, was 0.284/1000, which is significantly lower than the incidence rate for early cancerous events (*Boyes* 1969).

Thus, certainly a significant proportion, and probably the great majority, of precancerous lesions are not followed by invasive cancer of the cervix within the natural life span of the patient.

Other sources of information on the biologic significance of precancerous intraepithelial lesions are retrospective and prospective studies of patients. The retrospective studies are based on reviews of prior biopsies or smears in patients with a known clinical outcome.

The study by *Scipiades* and *Stevenson* (1938), cited in the preceding pages, is one of several papers on this subject. A recent retrospective study was published by *Kinlen* and *Spriggs* (1978), who obtained follow-up information on 60 patients with abnormal cervical smears obtained 2 or more years prior to the survey (mean interval, 5.2 years). Ten of the 60 patients (16%) developed invasive carcinoma, and five died of the disease. Three additional patients developed microinvasive carcinoma. In 19 of the remaining 47 patients, the follow-up smears or biopsies showed no residual lesion. In 20 patients there was evidence of persistent intraepithelial lesions on biopsy and in eight patients the smear was still abnormal, but a biopsy was refused. *Kinlen* and *Spriggs* also pointed out that the reversal to negative findings occurred more frequently in women less than 40 years of age.

Essentially similar results were obtained in a number of prospective studies. One of the most significant was the study conducted by *Peterson* (1955), who reported on the fate of 127 women with biopsy evidence of intraepithelial precancerous abnormalities of the uterine cervix that had been left untreated. Of these patients, 34 (26.8%) developed invasive cancer of the uterine cervix. The lesion disappeard in 30 (23.6%) patients and remained stationary in 50 (39.3%). A few patients were lost from this survey. Most important, perhaps, is *Peterson*'s report that it was not possible to prognosticate the outcome of intraepithelial lesions. Somewhat similar results were reported by this writer and his associates in 1963 as a result of a carefully conducted study of intraepithelial lesions. In 5 of 93 women, invasive cancer developed in spite of a very careful, personalized follow-up. In five additional women early invasion had probably occurred at the time of treatment. The lesions disappeared in 27 women for a period of 3 or more years and remained essentially unchanged in 56 patients. Again, it was emphasized that the histologic appearance of the epithelial lesions offered no prognostic guidance as to the behavior of the lesions. There are numerous additional studies which show essentially the same pattern of behavior: Regardless of histologic pattern, the lesions may either disappear, remain stationary for a number of years, or progress to invasive carcinoma.

II. Nomenclature of Precancerous Intraepithelial Lesions

Although the studies cited above clearly indicate that prognostication of intraepithelial lesions is not possible, the urge to reconcile the behavior of such lesions with cytologic and histologic patterns of the disease was a natural development in pathology. Thus, in 1953 *Reagan* et al. proposed that the intraepithelial lesions could be separated into two groups: carcinoma in situ and atypical hyperplasia or dysplasia. The differences were based on the cellular makeup of the epithelium: Lesions composed of small, poorly differentiated cells were classed as carcinoma in situ, while lesions made up of better differentiated cells, especially those with a tendency to form keratin, or lesions with keratinized surfaces, were classed as dysplasia. This nomenclature subsequently received the approval of an *International Committee* (1962). Very elaborate subclassifications of dysplasia based on cell and tissue patterns were later proposed (*Patten* 1978). It has been advocated by proponents of this system of nomenclature that the two groups of lesions have a different prognosis: Carcinoma in situ was the malignant

precursor of invasive cancer, whereas dysplasia was a benign lesion of uncertain prognosis, more likely to disappear than to progress (*Christopherson* 1969).

With the passage of time, several deficiencies of this concept were documented. It was clearly shown that invasive carcinoma may originate from well-differentiated vari-

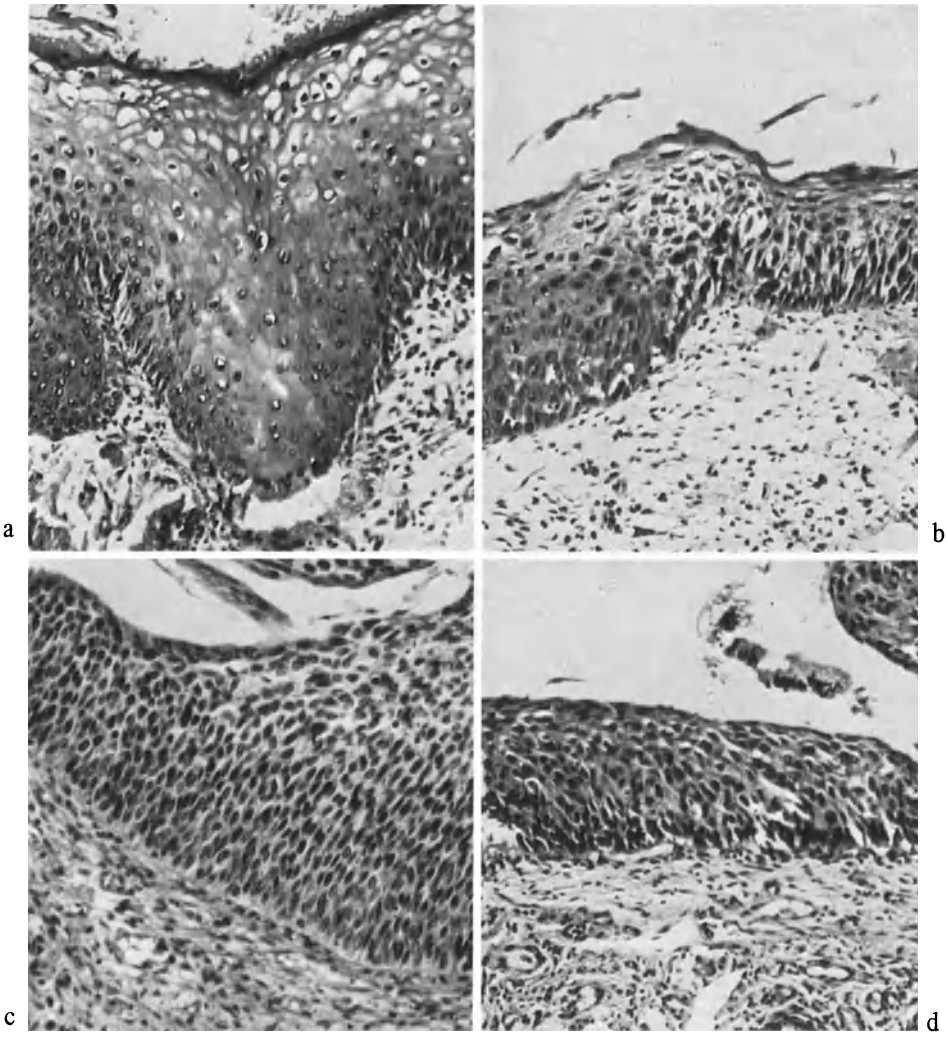

Fig. 9a–d. Various morphological aspects of cervical intraepithelial neoplasia involving squamous epithelium of the uterine cervix. The purpose of this group of photographs is to point out the fallacy of attempting to correlate the degree of morphological abnormality with clinical behavior. **a** Low-grade lesions (CIN grade I, mild dysplasia) which progressed to classical carcinoma in situ within 2 years. **b** More advanced lesion (CIN grade II, moderate dysplasia). The lesion persisted for 2.5 years and subsequently regressed. **c** Carcinoma in situ (CIN grade III). The lesion disappeared 2 months after biopsy. **d** Carcinoma in situ (CIN, grade III). The lesion persisted unchanged for 2 years and 2 months before treatment. **a–d**, × 150

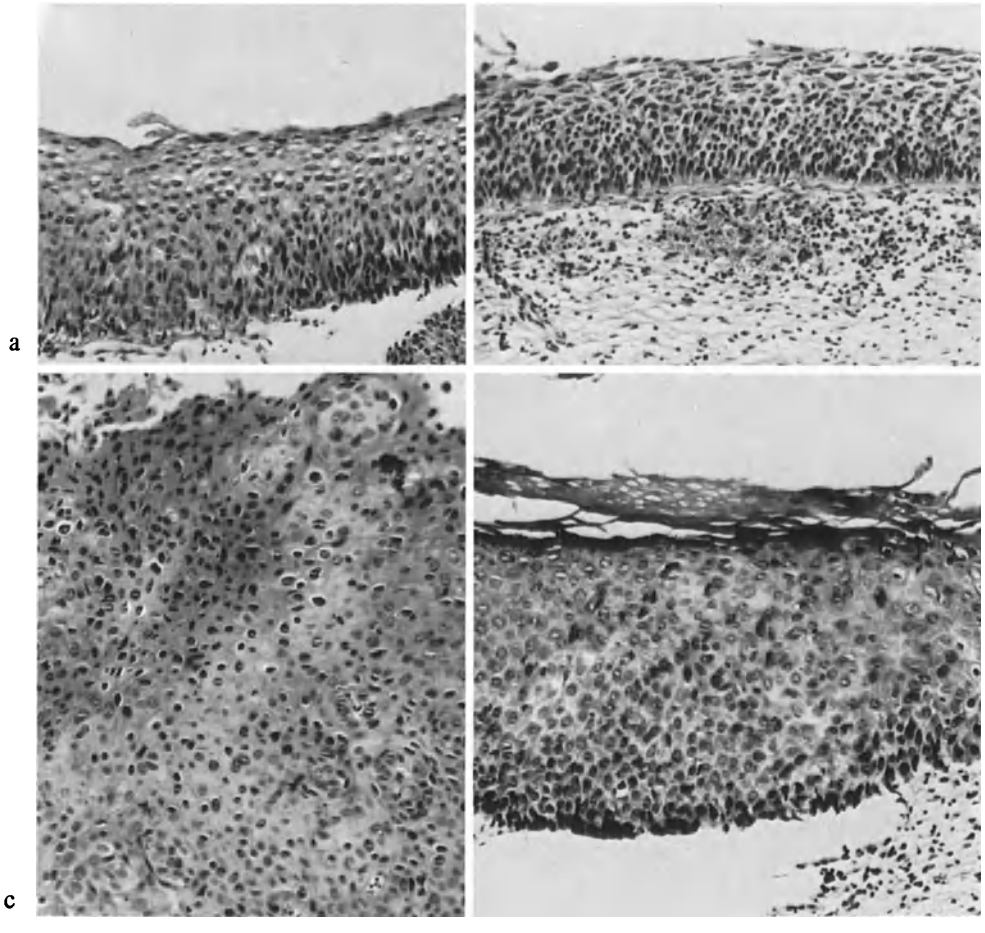

Fig. 10a–d. Several examples of intraepithelial lesions further illustrating lack of correlation between morphology and known behavior. **a** Carcinoma in situ, small cell type (CIN grade III). The lesion persisted unchanged for 5.5 years before treatment. There was no evidence of invasive carcinoma in cervical cone. **b** Carcinoma in situ, small cell type (CIN grade III). The lesion persisted unchanged for 7 years before treatment. No evidence of invasive carcinoma in cervical cone. **c** Keratinizing carcinoma in situ of portio vaginalis (CIN grade III). The lesion persisted unchanged for 4 years before treatment. There was no evidence of invasive cancer in cervical cone. **d** Keratinizing carcinoma in situ of portio vaginalis (CIN grade III). The lesion persisted unchanged for 4 years and then disappeared after a biopsy. **a–d,** × 150

ants of epithelial abnormalities, including those with keratinized surfaces (*Bangle* et al. 1963; *Burghardt* 1973). The follow-up studies, some of which were cited above, have shown that the histologic patterns of precancerous abnormalities are of no prognostic significance. Finally, the vagueness of the morphological definitions has accounted for major discrepancies in the interpretation of microscopic patterns (*Cocker* et al. 1968). Studies of DNA content (*Sachs* et al. 1972; *Wilbanks* et al. 1967), chromosomal abnormalities (*Granberg* 1971), and behavior in tissue culture (*Richart* et al. 1967) failed to disclose any basic differences that could be related to tissue pattern or prognosis of these lesions. For these reasons, *Richart* (1967) suggested that the term "Cervical intraepithelial neoplasia" (CIN) be used for the entire morphological spectrum of precancerous lesions in the uterine cervix. To satisfy the pathologist's need to define such lesions more precisely in terms of morphology, a system of grading was suggested, with CIN grade I corresponding to "mild dysplasia," CIN grade III to classical carcinoma in situ, and CIN grade II to intermediate lesions (*Koss* 1978). It must be clearly understood that this system of nomenclature calls for a careful clinical study of all patients with intraepithelial neoplasia, regardless of grade, and preferably with the use of the colposcope and colposcopically directed biopsies for further evaluation. The unpredictability of the clinical behavior of the histologic variants of intraepithelial neoplastic lesions and the difficulties of classification of such lesions are illustrated in Figs. 9 and 10.

III. Clinical Interpretation of Cellular Events in Carcinogenesis in the Uterine Cervix

The biologic and clinical evidence summarized in the preceding pages points out a number of very important facts about cancerogenesis in the epithelium of the human uterine cervix which are of considerable practical significance.

1. In the majority of patients the process of cancerogenesis is discontinuous.

2. The onset of the cancerous process observed at the cellular level merely indicates that the patient is at risk of developing further cancer, but the degree of risk cannot be estimated in any individual patient.

3. The process may be arrested or reversed at any time prior to the onset of invasive carcinoma, regardless of the morphological manifestations. Clinical evidence strongly suggests that the great majority of precancerous intraepithelial lesions will *not* result in clinical cancer during the life of the patient but will either regress or remain stationary. Nevertheless, such patients are at risk for the development of future lesions.

4. Progression to invasive carcinoma may occur along multiple morphological pathways: There may be a sequence of intraepithelial changes of increasing degrees of abnormality prior to invasion, or the initial morphologically inconspicuous changes in squamous epithelium may lead directly to invasive carcinoma. While some of these differences may be explained by anatomic location, the basic causes of invasive behavior are not understood at this time. Figure 11 illustrates these possibilities.

The question of whether this model of human cancerogenesis is also applicable to other organ systems cannot be answered at the moment. It is of interest, however, that studies of the bronchial tree in cigarette smokers by *Auerbach* et al. (1967) have disclosed the presence of precancerous epithelial abnormalities well in excess of the num-

ber of invasive bronchogenic carcinomas expected. The same may well apply, albeit on a more modest scale, to carcinogenesis in the human urinary bladder (*Koss* et al. 1969).

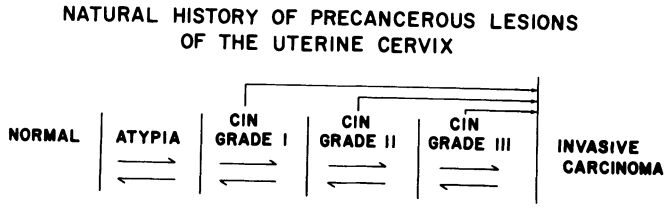

Fig. 11. Diagrammatic representation of several possible pathways of progression or regression of intraepithelial cancerous events in the uterine cervix (see text)

E. Critical Evaluation of Cervical Cancer Detection Systems

The concepts of pathogenesis of carcinoma of the uterine cervix outlined in the preceding pages have an important bearing on cervical cancer detection as currently practiced. For this reason, a critical evaluation of this problem appears warranted.

I. Principles of Cancer Detection

Theoretically, an efficient and cost-effective prevention program to deal with clinical cancer of any organ could be conducted if several important principles are observed:

1. The disease is relatively common in the target population.
2. The disease has a well-identified preinvasive stage.
3. Techniques of high specificity and sensitivity are available for the detection of the preinvasive stage.
4. The preinvasive stage of the disease can be treated efficiently in a cost-effective fashion, with no lowering of the patient's quality of life.
5. There is documented evidence that treatment of the preinvasive stage of the disease effectively reduces the incidence of invasive cancer.

Carcinoma of the uterine cervix fulfills all these criteria perhaps better than any other human cancer. The disease is reasonably frequent in various population groups, although the reported rates vary greatly from country to country for a variety of reasons, not all of which are fully understood at this time. Cancer of the uterine cervix has a well-known preinvasive stage which can be identified with considerable accuracy through cytologic screening. With the help of colposcopy, the preinvasive stage of the disease can be eradicated by conservative means, such as cryosurgery (*Tredway* et al 1972), cautery (*Nelson* et al. 1975), or conization (*Ahlgren* et al. 1975), usually with preservation of the patient's reproductive functions. Yet, the ultimate goal of eradication of carcinoma of the uterine cervix has not been achieved in any substantial population studied to date, although a major reduction in mortality has been well documented (*Christopherson* and *Scott* 1977; *Boyes* 1969). In fact, a number of reports from Sweden (*Rylander* 1976, 1977), New Zealand (*Green* 1966), and the United States (*Martin* 1972) call for a critical review of the entire costly procedure of cervical

cancer detection by cytology. It is, therefore, worthwhile to review the reasons for the partial failure of the detection programs.

II. Factors Accounting for Failure of Detection

1. The Target Population

It has been repeatedly shown that sexually active women from low economic strata more readily fulfill some of the epidemiologic factors that are conducive to cervical cancer than women from high socioeconomic brackets. It has also been shown that short of community measures specifically geared toward disadvantaged women, programs of cervical cancer detection fail to reach this most important target population (*Christopherson* and *Parker* 1969). Some communities also have significant problems in having such patients return for follow-up examinations. In a group of 76 patients with invasive cervical cancer (exclusive of microinvasive carcinoma), *Martin* (1972) considered patients' errors, such as failure to obtain an annual examination or refusal of a diagnostic procedure, as the most common preventable factor. The patients' errors, however, played a relatively minor role in *Rylander*'s report from Sweden (1976). It is obvious that patients' failures will continue to plague cancer detection programs and that carcinoma of the uterine cervix is not the only malignant disease subject to this problem.

2. Reliability of Cytologic Screening

a) Errors of Sampling

Several competent laboratories in various countries recorded the occurrence of invasive cervical cancer in women with previously negative or "atypical" smears (*Hφeg* and *Roger* 1968; *Figge* et al. 1970; *Rylander* 1976). An interesting light on the value of cervical cytologic sampling was shed by a series of recent papers, notably those by *Sedlis* et al. (1974) and *Luthy* et al. (1978), in which it was pointed out that two smears simultaneously obtained by competent clinicians are not of equal value. Contrary to the prevailing assumption that the first smear is more representative of the epithelial abnormality than the second one, it has been shown that the second smear contributes significantly to the discovery of precancerous lesions or cancer. The second smear increased the rate of detected severe abnormalities by 32.2% in *Sedlis*' report and by 19% in *Luthy*'s. In both instances, important lesions, such as carcinoma in situ or even invasive cancer, were missed either by the first or the second smear.

There is further evidence that smears may not be at all representative of the status of the malignant epithelium but instead show only "atypical" cells. This was recorded by *Figge* et al. (1970) and by *Nyirjersy* (1972) and repeatedly observed by this writer. There is also excellent evidence that during the course of follow-up of patients with important precancerous lesions, or even invasive cancer, smears may become free of abnormal cells (*Koss* et al. 1963). It has also been observed that second smears obtained a few days or weeks after the first abnormal smear are completely negative in

about 40% of such patients and thus give the patient and the gynecologist a false sense of security (*Koss* 1978). Both *Nyirjersy* (1972) and *Rylander* (1977) reported such events which, in *Rylander*'s experience, repeatedly led to invasive carcinoma. *Rubio* and *Lagerlöf* (1975) pointed out that an absence of shedding of abnormal cells from the surfaces of precancerous lesions may also be observed under ideal laboratory conditions. These observations on discontinuous shedding of abnormal cells have not been fully clarified. It may be speculated that the cells of the precancerous epithelium are not readily dislodged from the epithelial surface because they are bound to each other by well-developed desmosomes, as has been repeatedly demonstrated by electron microscopy (*Shingleton* and *Wilbanks* 1974). It is also possible that in some patients the morphological abnormalities of cells commonly associated with precancerous states or cancer may be absent on the epithelial surface. This possibility would suggest that cancerous epithelium is intermittently capable of producing morphologically normal surface cells, or at least cells with morphological abnormalities too subtle to be identified under the light microscope. It is also possible that both options may coexist. In any event, the notion that a cervical smear is at all times representative of the epithelial abnormality is not correct. It has been shown by *Naujoks* et al. (1976) that even the most careful clinical sampling by several methods combined (cervical scrape smear, endocervical aspiration) still fails to detect a proportion of precancerous lesions.

These observations must inevitably lead to a new strategy for developing the most effective application of resources in the screening of patients for cancer of the uterine cervix. This strategy will be discussed later.

b) Errors of Interpretation

α) Errors in Clinical Interpretation of Laboratory Data

Evidence has been presented in this chapter that the majority of precancerous lesions of the uterine cervix are unlikely to progress to invasive cancer during the lifetime of the patient. Evidence has also been presented to show that the morphological configuration of the precancerous epithelium offers little, if any, opportunity for the precise prognostication of future behavior. Nevertheless, the old classification of precancerous lesions as "dysplasia," with allegedly good prognosis, and "carcinoma in situ," with allegedly bad prognosis, lingers on. Consequently, invasive cancers have been repeatedly observed in patients with "mild dysplasia" (*Burghardt* 1973).

Another important source of error is the assumption that cytology accurately reveals the status of the epithelium and that it is reliable as a follow-up procedure. This is not the case. Clinical action, such as colposcopy, must be initiated on the basis of the first abnormal smear without wating for confirmatory evidence. In several of the cases of invasive carcinoma reported by *Rylander* (1976), the patient was not followed because the second smear was negative. It was thus assumed that the first smear, which had disclosed an abnormality, was in error.

Finally, it must be recognized by the clinician that in many lesions the cytologic evidence of disease is only minimal and that it will be reported in a nonspecific fashion as "atypia." If there is no obvious reason for the abnormality, such as an inflammatory

process or some form of prior treatment, the patient should have the benefit of a careful colposcopic evlauation.

β) Laboratory Errors

Interpretation of the cytologic sample. It is not the purpose of this summary to describe the many difficult aspects of interpretation of cytologic material from the uterine cervix. Other sources must be consulted on this subject (*Patten* 1978; *Koss* 1979). It must be pointed out, however, that the detection of precancerous states and cancer of the uterine cervix is often based not on classical smear patterns, but on trivial evidence confined to a few cells with abnormal nuclear features. In laboratories with limited diagnostic experience, this evidence is often overlooked, disregarded, or minimized, and reported as "atypia" or in an equivalent manner. As has already been pointed out, such patients deserve a careful examination, including colposcopy, to rule out the presence of an important lesion.

The introduction of a *quality control system* of cytologic screening is equally important. Federal health authorities in the United States suggest a rescreening of 10% of smears by another observer. This probably represents a minimum of care in the interpretation of the smears. Excellent training of cytotechnologists and postgraduate education are equally important to insure the high quality of diagnostic performance. Simultaneous colposcopy and cytology (*Naujoks* et al. 1976) are other important quality control systems.

Interpretation of the biopsy. In the part of this chapter devoted to the terminology and clinical significance of tissue patterns, it was pointed out that no prognostication is possible on the strength of the histologic appearance of epithelial abnormalities. Unfortunately, the interpretation of tissue and cell patterns often rests in separate hands, although the two appraoches to the diagnosis of cervical cancer are complementary. There is ample evidence, previously cited (*Koss* 1978), that the classification of lesions varies enormously depending on the experience and education of the observer. With the passage of time and improved correlation and long-term follow-up experience, a more aggressive approach to the interpretation of cervical biopsies is usually adopted. It is important for the pathologist to maintain open channels of communication with the clinician, who should be an experienced colposcopist. Thus, not only the degree of cytologic and histologic abnormality, but also the size and the location of the lesion can be considered before definitive treatment is planned.

III. Suggested Strategy for Cost-Effective Screening for Cancer of the Uterine Cervix

In view of the significant percentage of failures in the discovery of premalignant lesions by cytologic techniques, it appears reasonable to conclude that several cytologic samples are required to determine that the patient is free of disease. This could be established either by three consecutive smears at intervals of 6–12 months or by two screening procedures, each composed of two separately obtained smears. The first ab-

normal sample suggestive of a neoplastic abnormality should trigger further clinical investigation, including a careful colposcopic examination of the cervix.

Subsequent follow-up procedures may be individualized. Patients who, for reasons of epidemiologic characteristics, are likely to develop a precancerous lesion should probably undergo a reexamination every 2 years. Patients who do not have such epidemiologic characteristics could be reexamined every 3rd or 4th year. These suggestions are at best tentative, since no hard data exist to support these theoretical considerations.

It is evident that a large percentage, and probably the majority, of precancerous lesions are not likely to progress to invasive carcinoma; thus, every care should be taken to treat such lesions with a minimum of trauma and, if the patient so desires, with preservation of her genital tract. Thus, in the absence of invasion, hysterectomy should be considered a treatment of last resort. It is perfectly evident that for many patients the treatment in whatever form is not justified by the biologic facts. However, until methods of prognostication are established, every patient with a precancerous lesion must be considered at risk of developing cancer of the uterine cervix and must be treated accordingly.

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Structural Variations of Cervical Cancer and Its Precursors Under the Influence of Exogenous Hormones

G. DALLENBACH-HELLWEG

Besides the widespread use of hormones for contraception, pure estrogens are given to relieve menopausal symptoms and progestogens are prescribed for the treatment of endometriosis and endometrial carcinoma. In recent years this has provided opportunities for studying certain structural differentiations which emerge during the process of carcinogenesis in the cervix. These observations are based on prolonged study of the different effects of estrogens and progestogens on the squamous epithelium of the ectocervix and the mucosa of the endocervical canal. Estrogens stimulate proliferation of the stratified squamous epithelium of the ectocervix, but not that of the columnar epithelium of the endocervix. Progestogens stimulate the columnar epithelium and the reserve cells beneath it, but not the squamous epithelium. When an epithelial defect develops on the external surface of the cervix because of erosion of the vulnerable columnar epithelium that has grown out at that site as the result of ectopia, under *estrogenic stimulation* it becomes reepithelialized mainly by the stratified squamous epithelium: the defect is covered by *regenerative epithelium* (Fig. 1), which grows

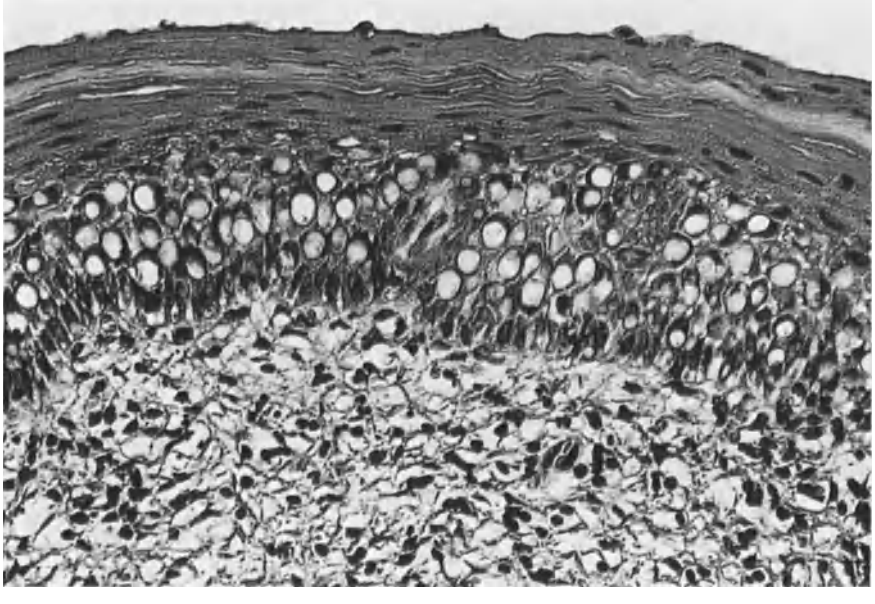


Fig. 1. Regenerative epithelium of the ectocervix. Maturation is inadequate and stratification is only just visible; a broad zone of parakeratosis covers the area. PAS, × 370

over it from outside and spreads upward, i.e., from the external surface into the cervical canal. Under conditions of *progestogenic stimulation,* on the other hand, proliferation of the reserve cells of the cervical mucosa in the form of *reserve cell hyperplasia* (Fig. 2) often precedes regeneration of the squamous epithelium. That

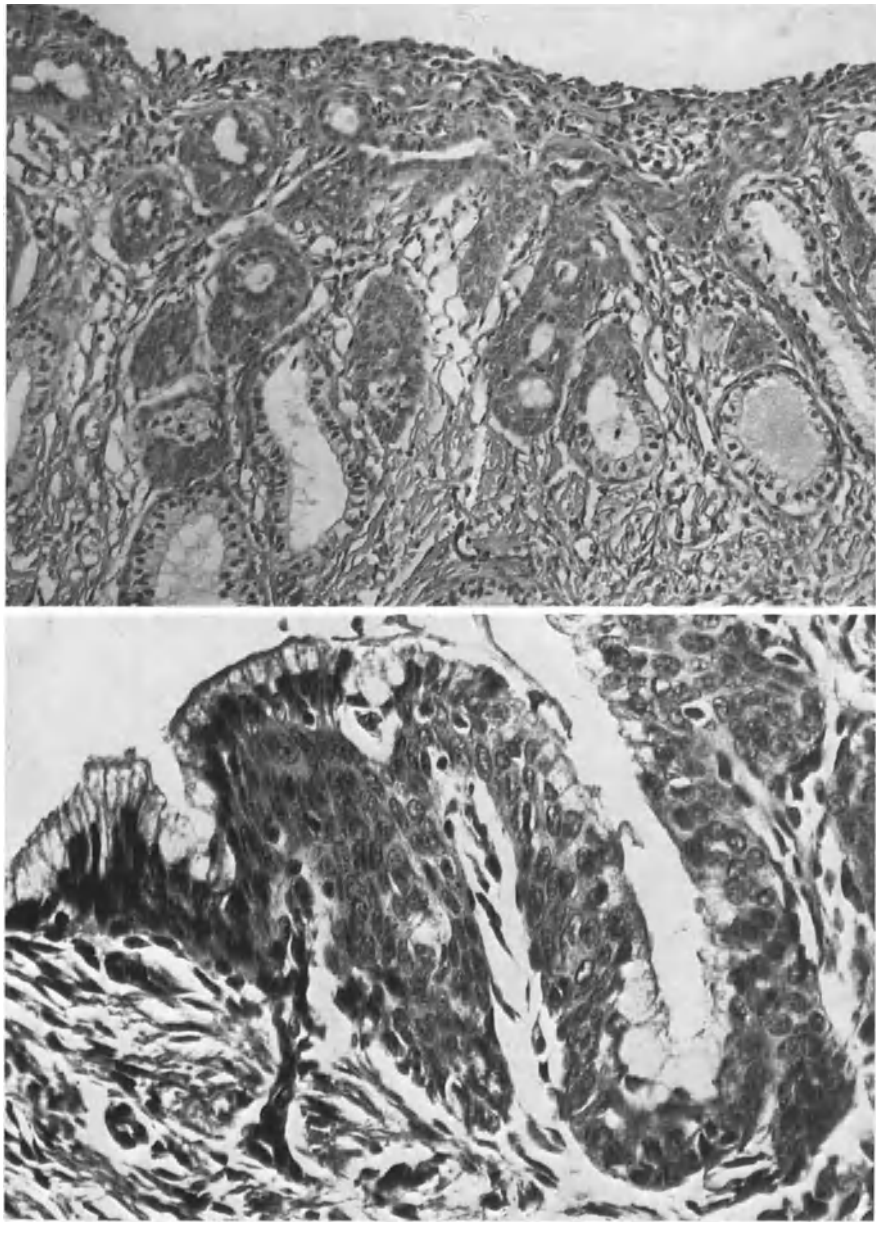


Fig. 2a, b. Reserve cell hyperplasia of the endocervical mucosa; **a** in the vicinity of the glands and extending from there on to the surface lesion; **b** of the surface epithelium with formation of downgrowths. H & E: **a** × 190; **b** × 370

reserve cell hyperplasia spreads over the defect from above downward, i.e., from the cervical canal towards the vaginal portion of the ectocervix, then undergoes maturation through the process of squamous metaplasia. Up to this point we have been dealing with benign repair processes, which make up by far the largest proportion of all the phenomena of reepithelialization and healing seen in cervical ectopia. The last stage of this healing process is signaled by the appearance of the so-called *third mucosa* on the vaginal portion of the cervix (Fig. 3). That consists of cervical mucosa covered by a layer of mature stratified squamous epithelium, the cervical glands having been pinched off with the formation of retention cysts in some cases. At this stage it is no longer possible to determine whether the squamous epithelium has originated from regenerative epithelium or from reserve cell hyperplasia.

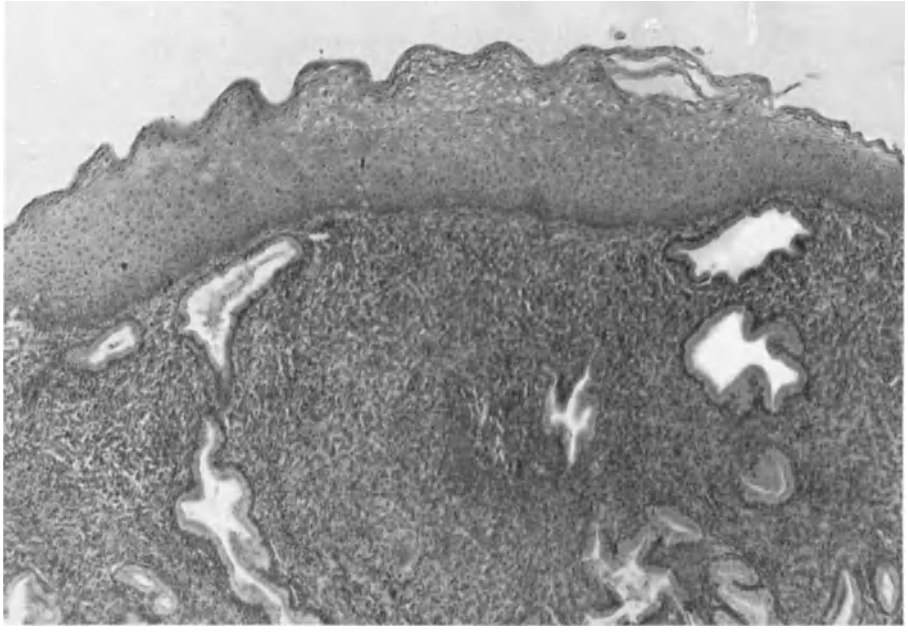
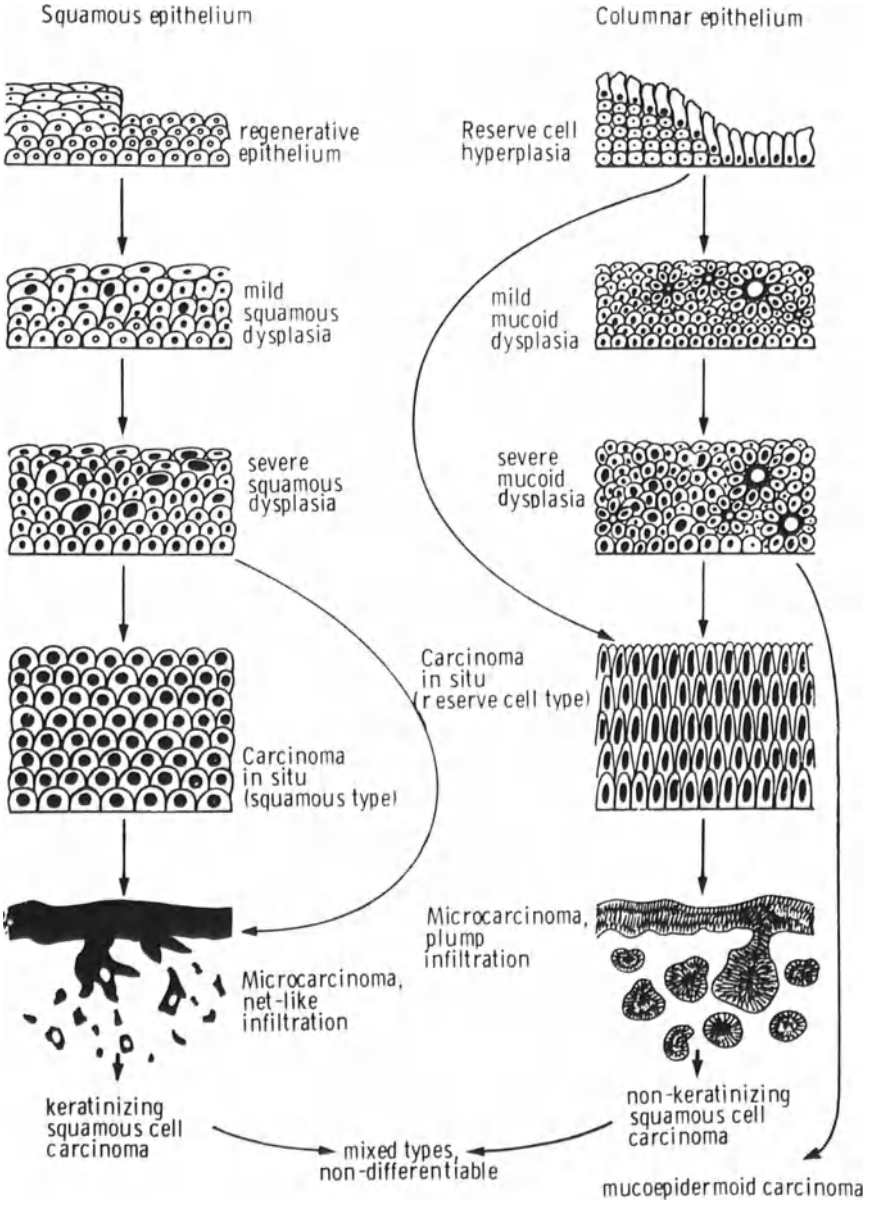
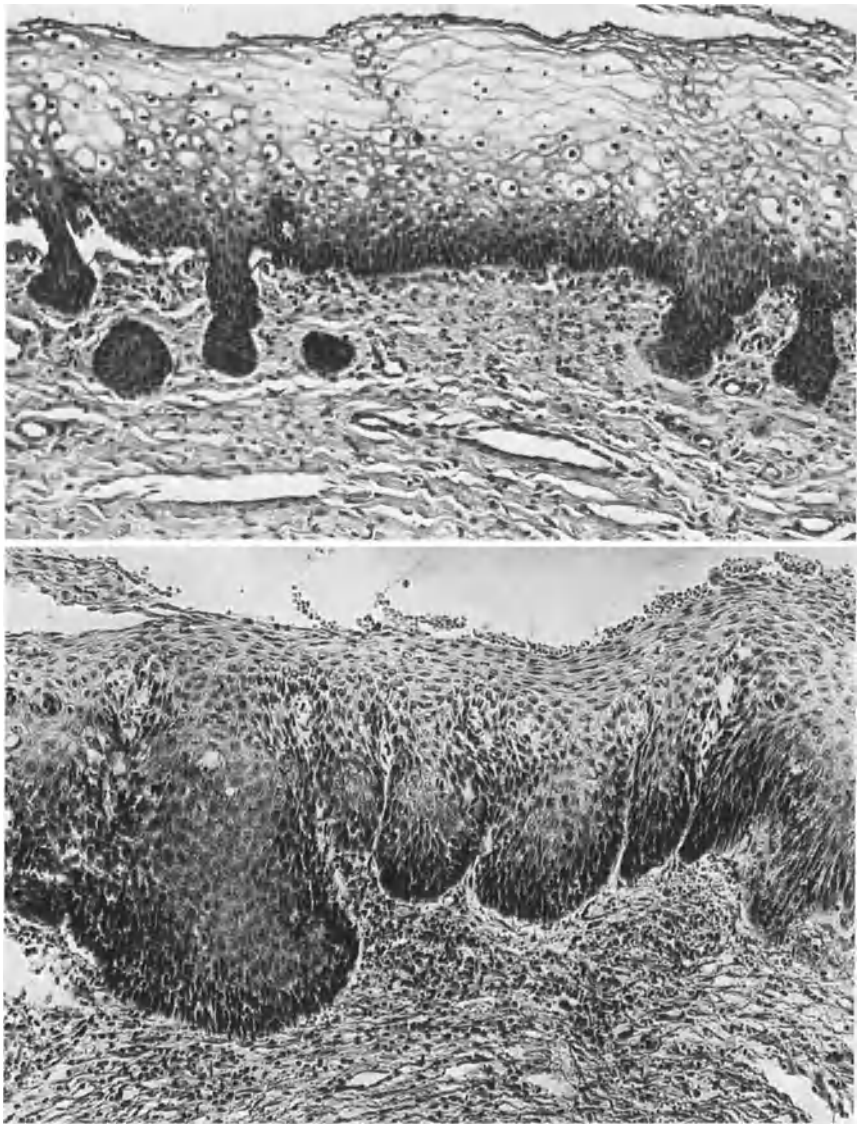


Fig. 3. So-called *third mucosa;* normally maturing stratified squamous epithelium on the ectocervix, overlying nipped off cervical glands (an inflammatory erosion which has healed and reepithelialized). H & E, x 60

In a small percentage of cases, however, reepithelialization does not proceed smoothly to normal maturation of the overgrowing epithelium; on the contrary, it is followed by the development of precancerous lesions of various grades (Table 1). In such instances the prolonged increase in proliferative activity has prepared the way for carcinogenic substances to manifest their effects. From the appearance of the various forms of intraepithelial neoplasia it is possible to determine the cells from which they originated. For example, *dysplasias and carcinoma in situ of the squamous type* develop from regenerative epithelium derived from the stratified squamous epithelium of

Table 1. Diagram of carcinogenesis in the cervix, arising from the regenerative epithelium of the ectocervix *(left column)* or from the reserve cells of the endocervical mucosa *(right column)*. The arrows indicate the sequence of developments and the possible shortcuts between separate stages.



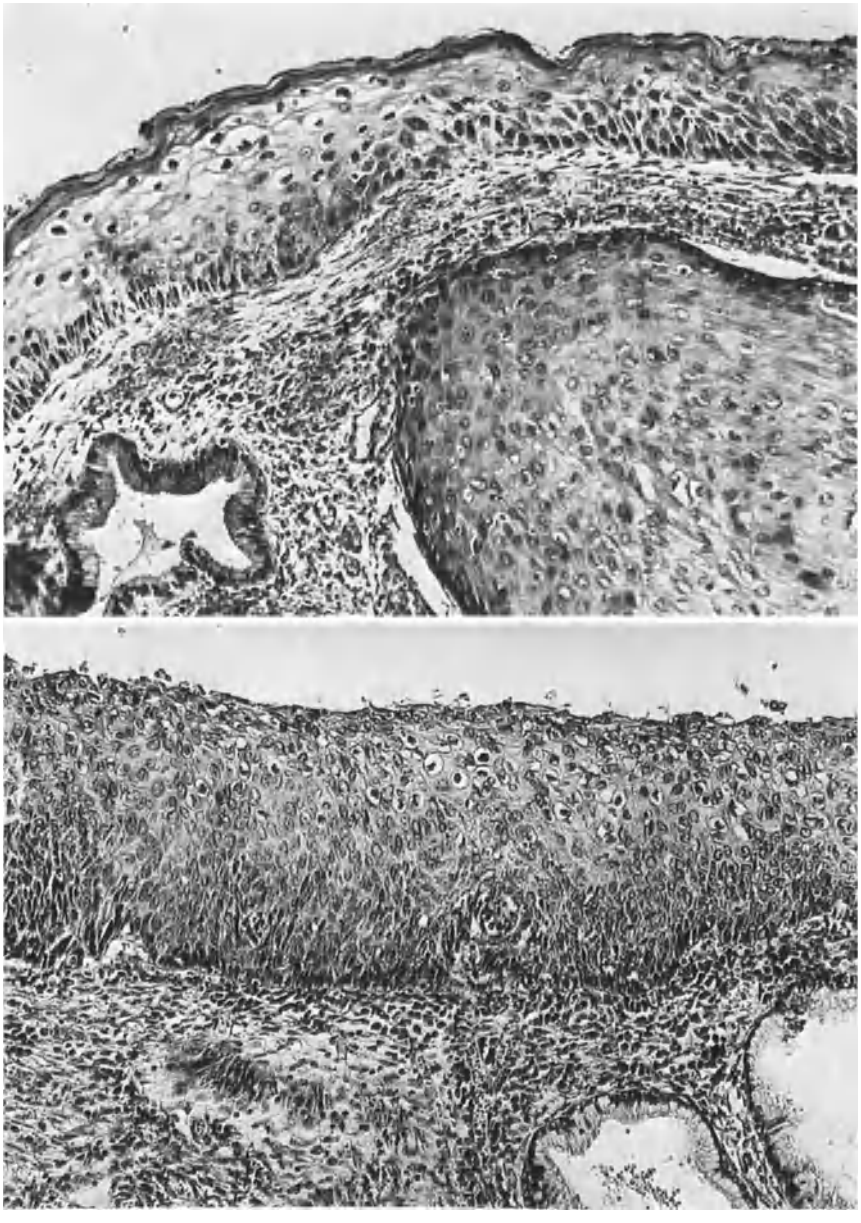


a

b

Fig. 4a, b. **a** Mild, **b** moderately severe dysplasia of squamous cell type, arising in each instance from downgrowths from the basal layer, while the upper layers of epithelium are still maturing normally. H & E: **a** × 150; **b** × 150

the ectocervix, i.e., from plump, rounded cells with round, often polyploid, nuclei (Figs. 4–9). Stratification is largely or completely lost, while the superficial layers show atypical parakeratosis (estrogen effect!), and there is considerable basal activity, as reflected by the formation of broad pegs of cells extending into the stroma as bulky outgrowths (Fig. 9). At the same time there may also be a pronounced spread of the epithelium in the form of papillomatous dysplasia (Fig. 7).



a

b

Fig. 5a, b. **a** Mild, **b** moderately severe dysplasia of squamous cell type. Nuclear polymorphism and hyperchromasia in all layers. Stratification is still clearly recognizable in **a** but only faintly apparent in **b**. H & E: **a** × 150; **b** × 150

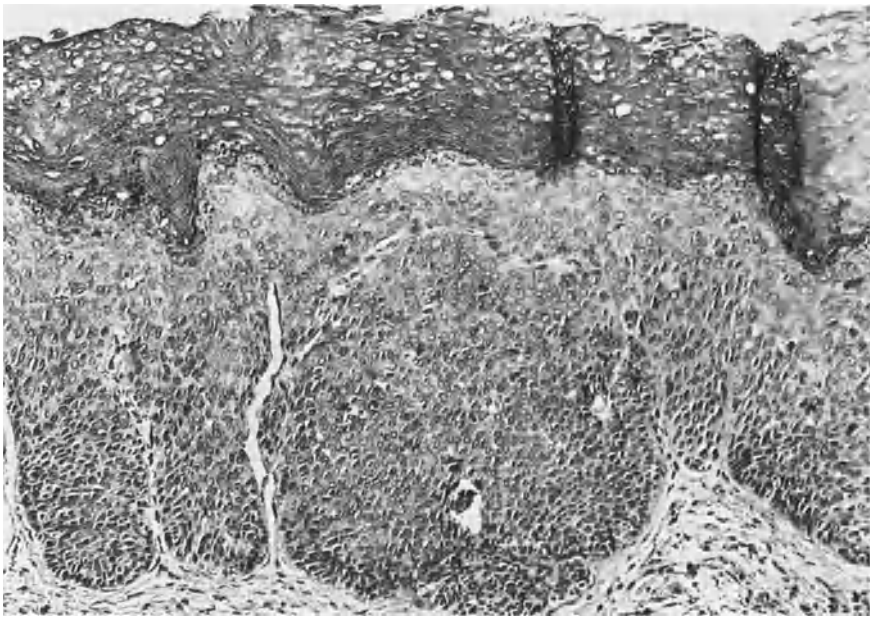


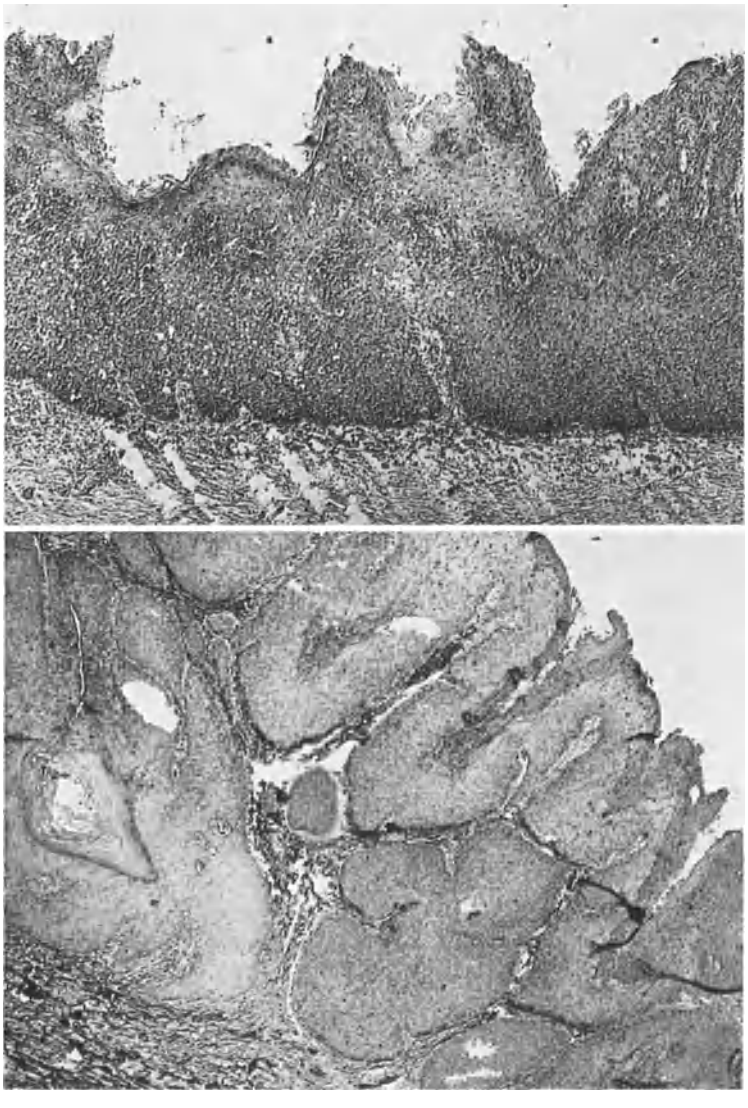
Fig. 6. Severe dysplasia of squamous cell type. Stratification largely abolished, considerable widening of epithelial layer with distinct formation of downgrowths, severe nuclear and cellular polymorphism, and a broad zone of overlying parakeratosis. PAS, × 150

The spread of this atypical epithelium is often confined to the surface of the ectocervix, though it sometimes penetrates from there into the necks of the endocervical glands.

On the other hand, *mucoid dysplasia and carcinoma in situ of the reserve cell type* develop on the basis of reserve cell hyperplasia (Figs. 10–13). They are characterized by long, spindle-shaped cells containing elongated nuclei which are very chromatin dense, but uniform. One striking feature is the large proportion of cells in mitosis, with a predominance of three-group metaphases among the abnormal forms (see *Hamperl* 1965). During the dysplastic stage, mucoid substances may still be detectable in the cytoplasm, sometimes in the form of unicellular mucoid degeneration (Fig. 10). This epithelium is found chiefly in the endocervical canal and the vicinity of the external os and often fills the cervical glands completely (Fig. 13). It is hence somewhat more difficult to pick up by cytological screening methods than the intraepithelial neoplasia derived from squamous epithelium.

With regard to the meaning and significance of these two abnormalities, the comment made by *Koss* in this volume is undoubtedly true: "Prognostication of intraepithelial lesions is not possible at the cervix."

If a carcinoma develops from this neoplasia, such a tumour in its initial stage of *microcarcinoma* can still be traced back to the cell type from which it originated. When invasion begins, intraepithelial neoplasia of the squamous type ramifies at an early stage into net-like formations, though differentiation with a tendency to keratin-



a

b

Fig. 7a, b. Papillomatous dysplasia of the ectocervix with pronounced thickening of the squamous epithelium. **a** The papillae are predominantly superficial. **b** Papillary structures extending into the stroma with a broad overlying zone of parakeratosis. H & E, x 60 (**a** and **b**)

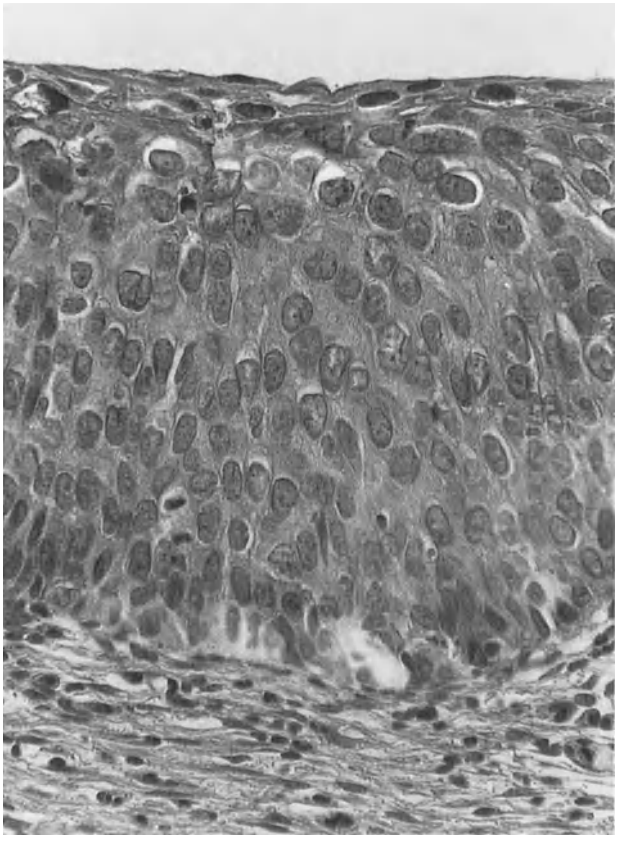


Fig. 8. Carcinoma in situ of squamous cell type: simple replacement. Stratification completely abolished, cellular and nuclear immaturity with mitoses in all layers. Narrow overlying zone of atypical parakeratosis. The patient had taken sequential oral contraceptives for many years. H & E, × 370

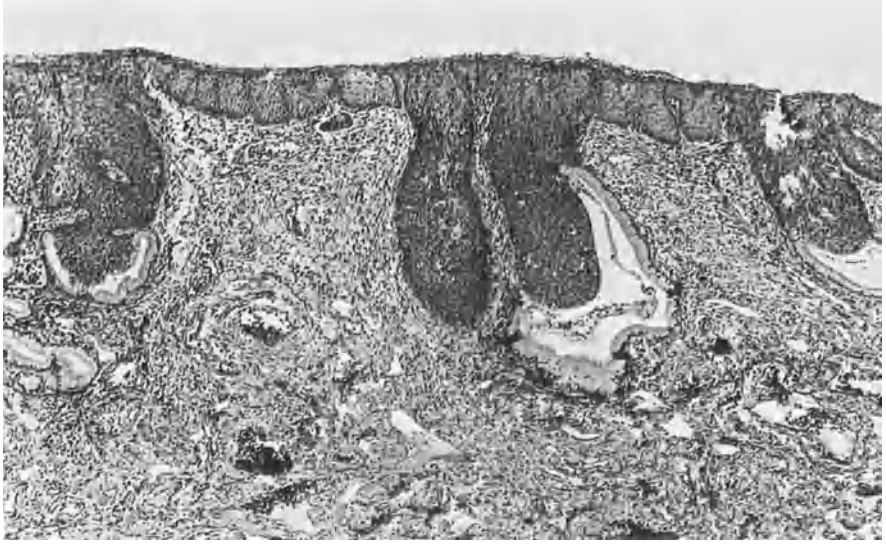
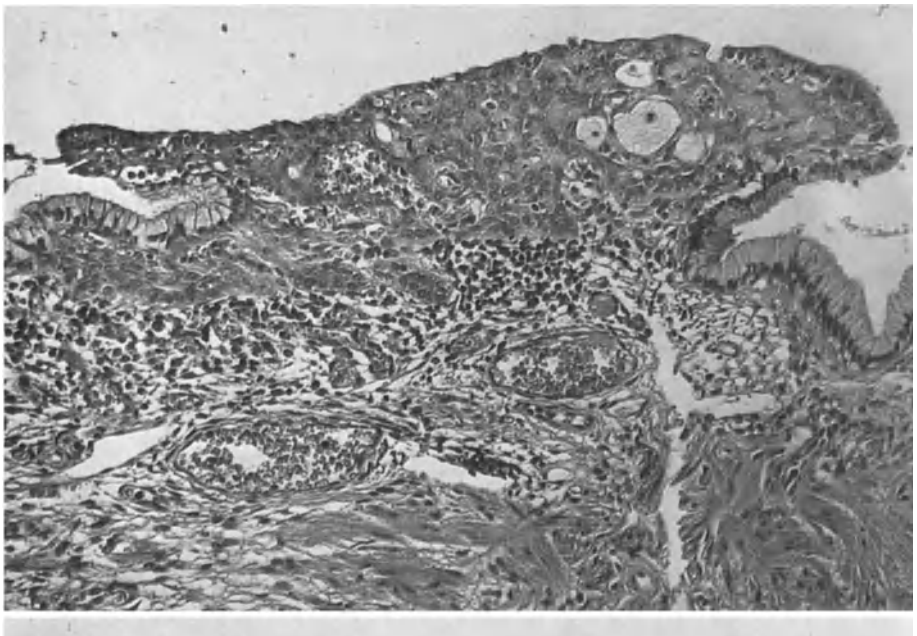


Fig. 9. Carcinoma in situ at the stage of bulky outgrowth. Squamous cell type. Complete abolition of stratification, marked nuclear and cellular immaturity in all layers, especially in the vicinity of the downgrowths. H & E, × 60



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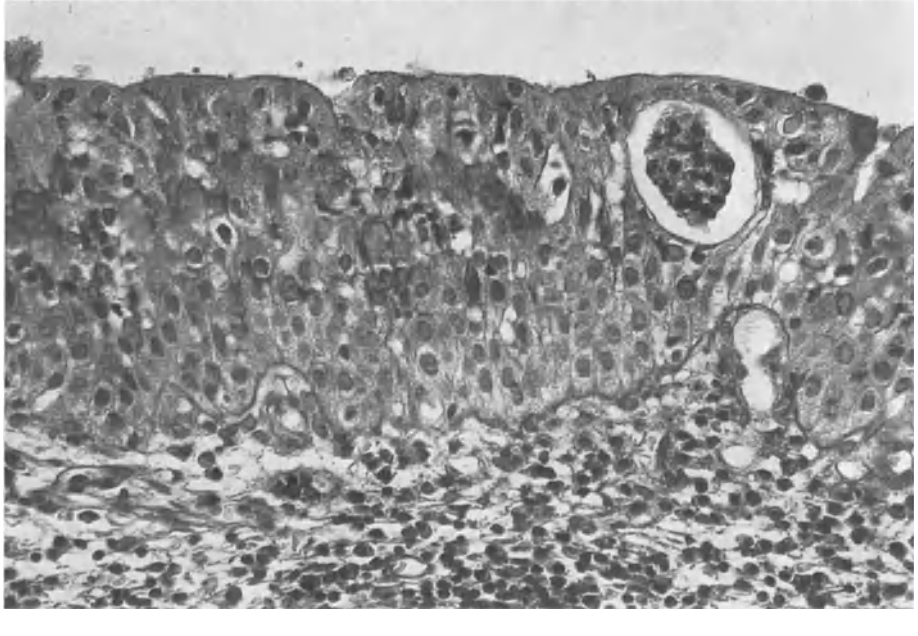

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Fig. 10a, b. Mild mucoid dysplasia, reserve cell type. Nuclear and cellular polymorphism in all layers. Single-cell mucoid change shows that this epithelium is derived from the mucus-secreting columnar epithelium of the endocervix. H & E: **a** × 190; **b** × 370

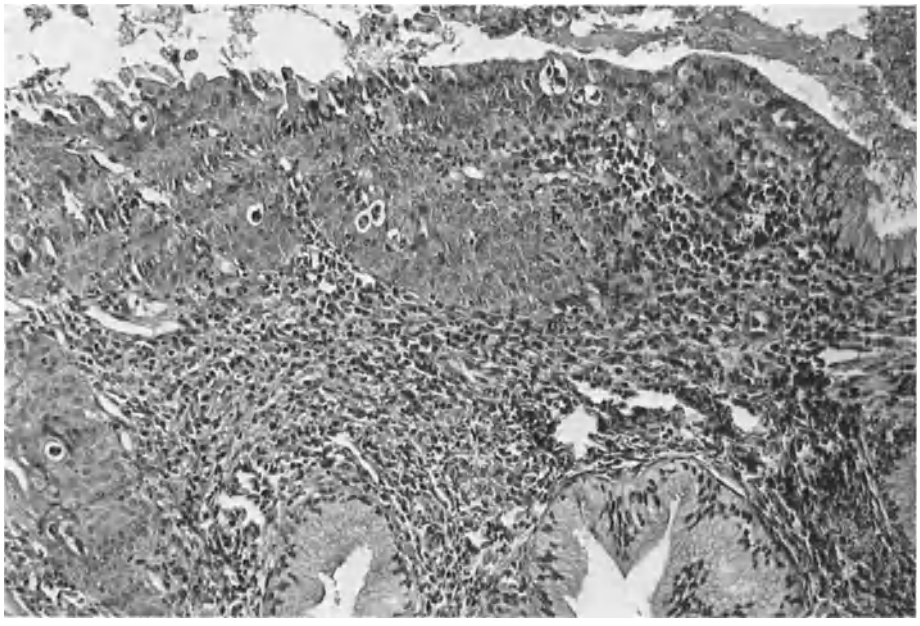

Fig. 11. Severe mucoid dysplasia, reserve cell type. Stratification is largely abolished and there is still considerable nuclear and cellular polymorphism, but the cells are increasingly immature. Scattered single-cell mucoid change. Pronounced stromal reaction. H & E, x 150

ization may appear at the invasion front (Fig. 14). In such circumstances the grade of intraepithelial neoplasia previously reached is of no significance; early invasion can follow directly upon moderately severe dysplasia, with the stage of carcinoma in situ being omitted or leapfrogged (Fig. 15). One characteristic feature is the intense stromal reaction which surrounds such areas.

In consequence of their early *splitting up into net-like structures,* the carcinoma cells soon establish connections with lymphatic and vascular spaces and hence tend to metastasize at an early stage. This form of microcarcinoma hence demands radical measures and should be treated by Wertheim's hysterectomy.

Those microcarcinomas that develop from a carcinoma in situ of the reserve cell type display a different pattern of stromal infiltration. They form *rounded columns* of cells which do not ramify until they have reached a late phase and have spread far beyond the bounds of a microcarcinoma (Fig. 16). At times when the region of endocervical glands has greatly expanded under the progestogen effect, and the rounded columns of tumor cells extend deeply into them, the columns give the impression that they have penetrated beyond the mucosa and are invading the muscle wall of the cervix. Since that invasion is only apparent and not real, the prognosis is more favorable with regard to metastases. In general, a simple hysterectomy suffices for complete removal of the tumor.

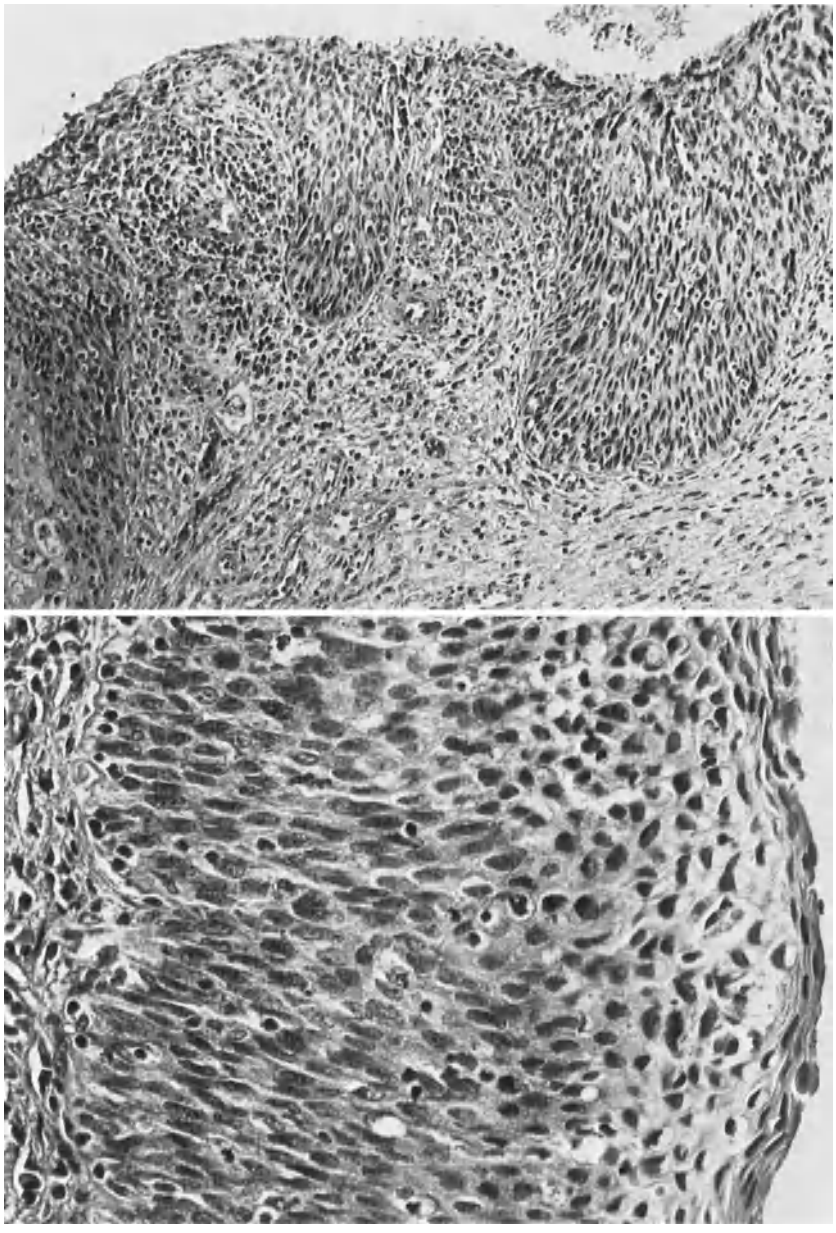

Fig. 12a, b. Carcinoma in situ, reserve cell type. Superficial spread with **b** simple replacement and **a** downgrowth formation. Elongated, spindle-shaped nuclei are conspicuous, stratification is abolished, nuclear and cellular immaturity of extreme degree, numerous mitoses. The patient had taken an oral contraceptive containing Norgestrel for 10 years. H & E: **a** × 150; **b** × 370

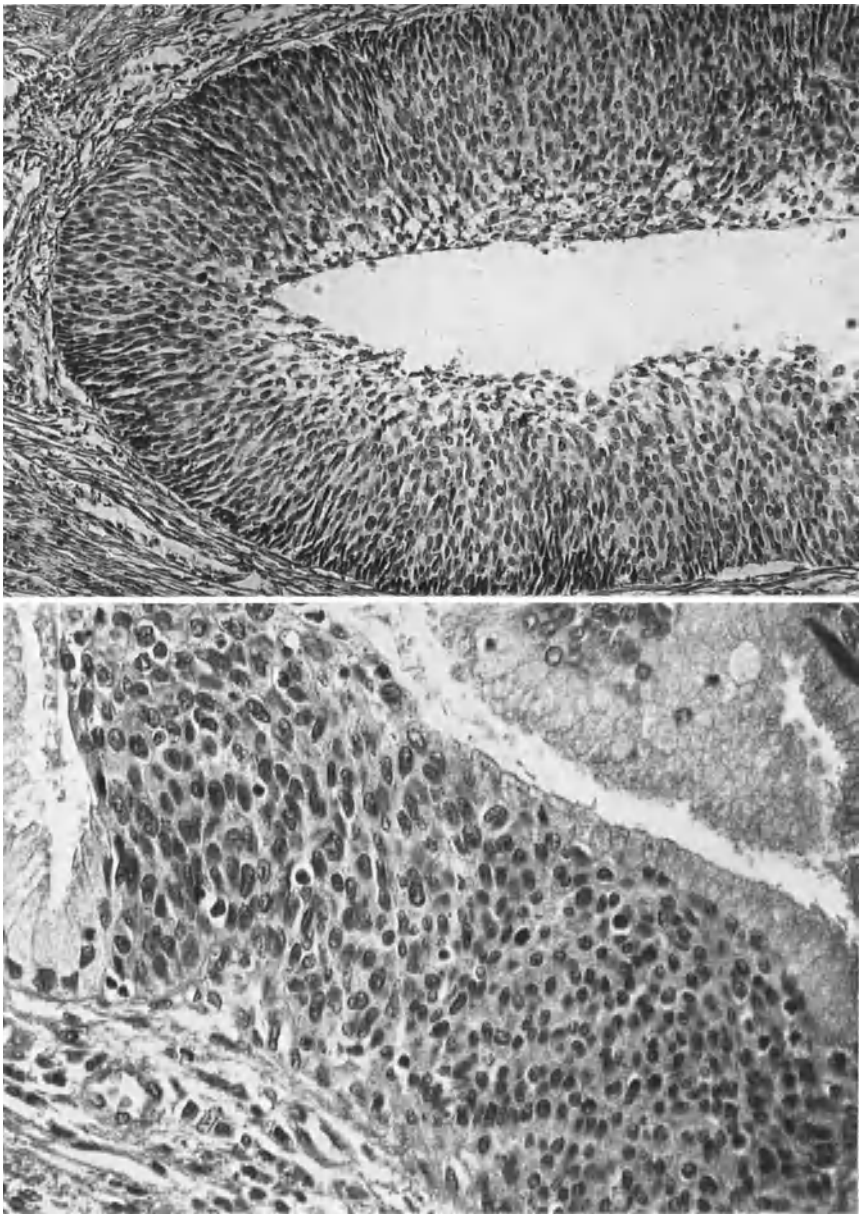

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Fig. 13a, b. Carcinoma in situ, reserve cell type, replacing glandular epithelium. Stratification completely abolished, marked nuclear and cellular immaturity; the elongated, oval, spindle-shaped nuclei are conspicuous. The patient had taken an oral contraceptive containing Norgestrel for 10 years. H & E: **a** × 150; **b** × 370

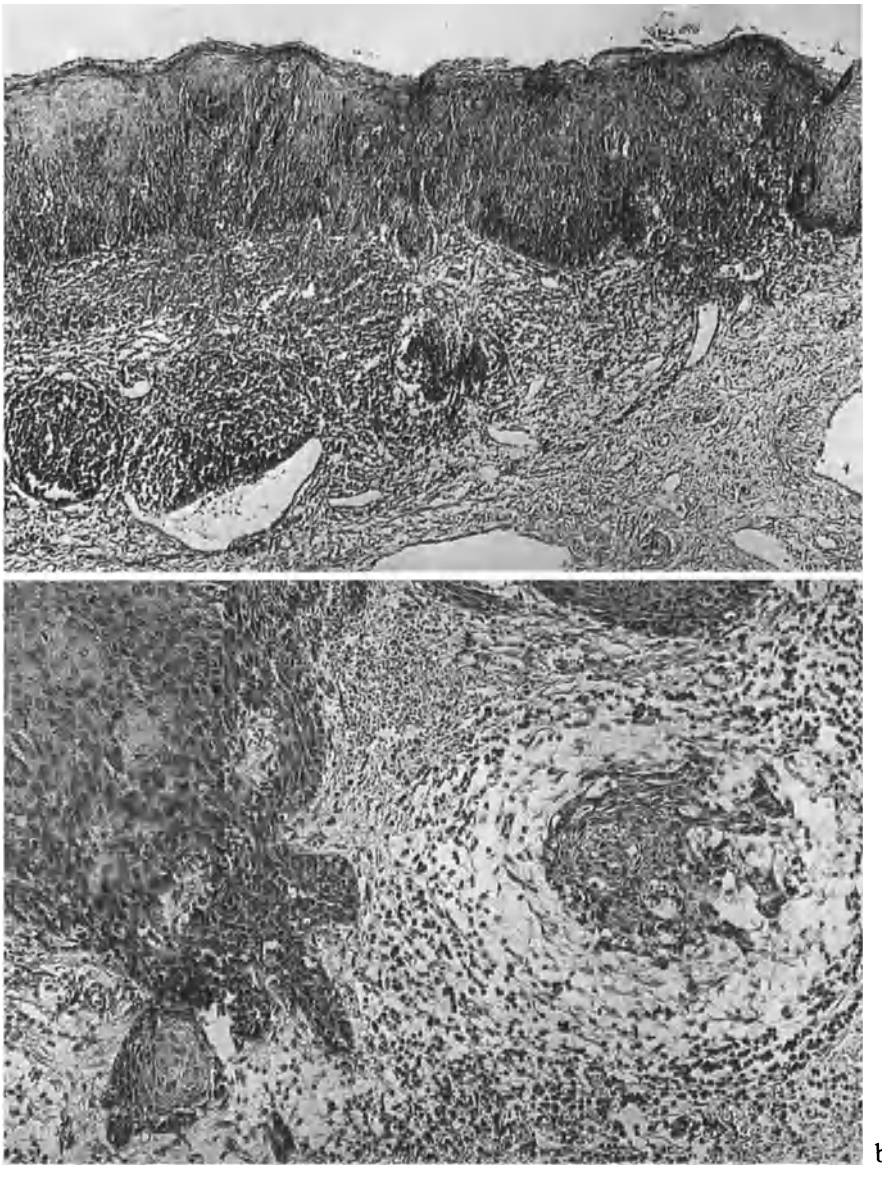

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Fig. 14a, b. Microcarcinoma with net-like infiltration, arising from a carcinoma in situ of squamous type. Conspicuous stromal reaction in the vicinity of the cell clumps which have split off and extended down from the basement membrane. H & E: **a** × 60; **b** × 150

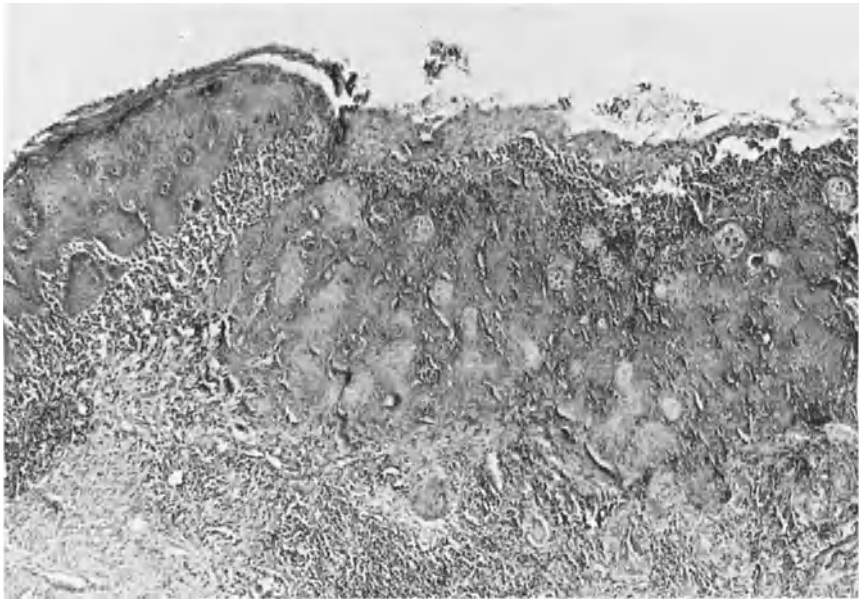

Fig. 15. Microcarcinoma of squamous cell type arising from an area of dysplasia. There is some tendency toward maturation as shown by areas of incipient keratinization in the vicinity of the downgrowths, which form net-like infiltration at some points. H & E, × 60

When a *squamous carcinoma* has reached the stage of *widespread invasion,* it is usually impossible to recognize the cell type from which it originated. This applies in particular to the majority of *nonkeratinizing* squamous carcinomas (Fig. 17). In contrast, *keratinizing* squamous carcinomas (Fig. 18) can be traced back to the stratified squamous epithelium of the ectocervix, while the cylindromatous form (Fig. 19) arises from the reserve cells of the endocervical epithelium.

Mucoepidermoid carcinomas (Fig. 20) represent a mixture of both elements, and their formation is usually preceded by intraepithelial neoplasia of both cell types. Indeed, such a combination is not infrequently observed. The characteristic location of this type of carcinoma – at the junction between the two kinds of epithelium – implies that both epithelial elements will be involved in the makeup of the carcinoma. But it must also be remembered that, especially in this location, the precursor cells are pluripotential: just as the squamous cell of the ectocervix (before it has been committed to its preordained potential) is still capable of producing mucus, so can the reserve cells of the cervical mucosa in this precursor phase occasionally develop into keratinizing squamous cells, even though the overwhelming majority are predestined to differentiate into mucus-secreting columnar cells (cf. *Stegner,* S. 181). The prospective potentiality of a young cell thus extends beyond its prospective significance, a fact that provides a good explanation for the occurrence of mucoepidermoid carcinoma of the squamocolumnar junction, which make up roughly 7% of all squamous carcinomas of the ectocervix (*Hellweg* 1957). *Clear-cell carcinomas* of the ectocervix

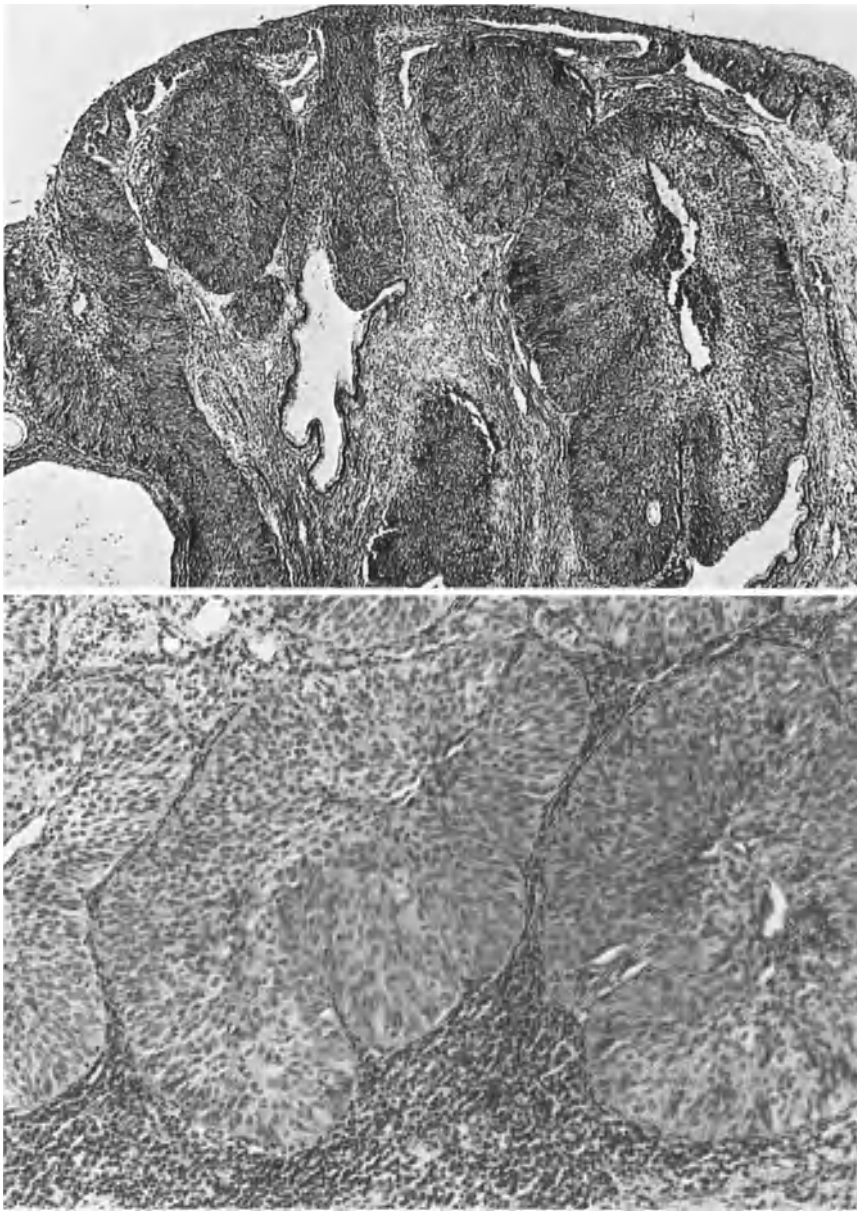

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Fig. 16a, b. Microcarcinoma of reserve cell type with plump infiltration in the vicinity of the greatly extended cervical gland field. Stratification is completely abolished and there is no differentiation; the elongated nuclei are obvious. H & E: **a** × 60; **b** × 150

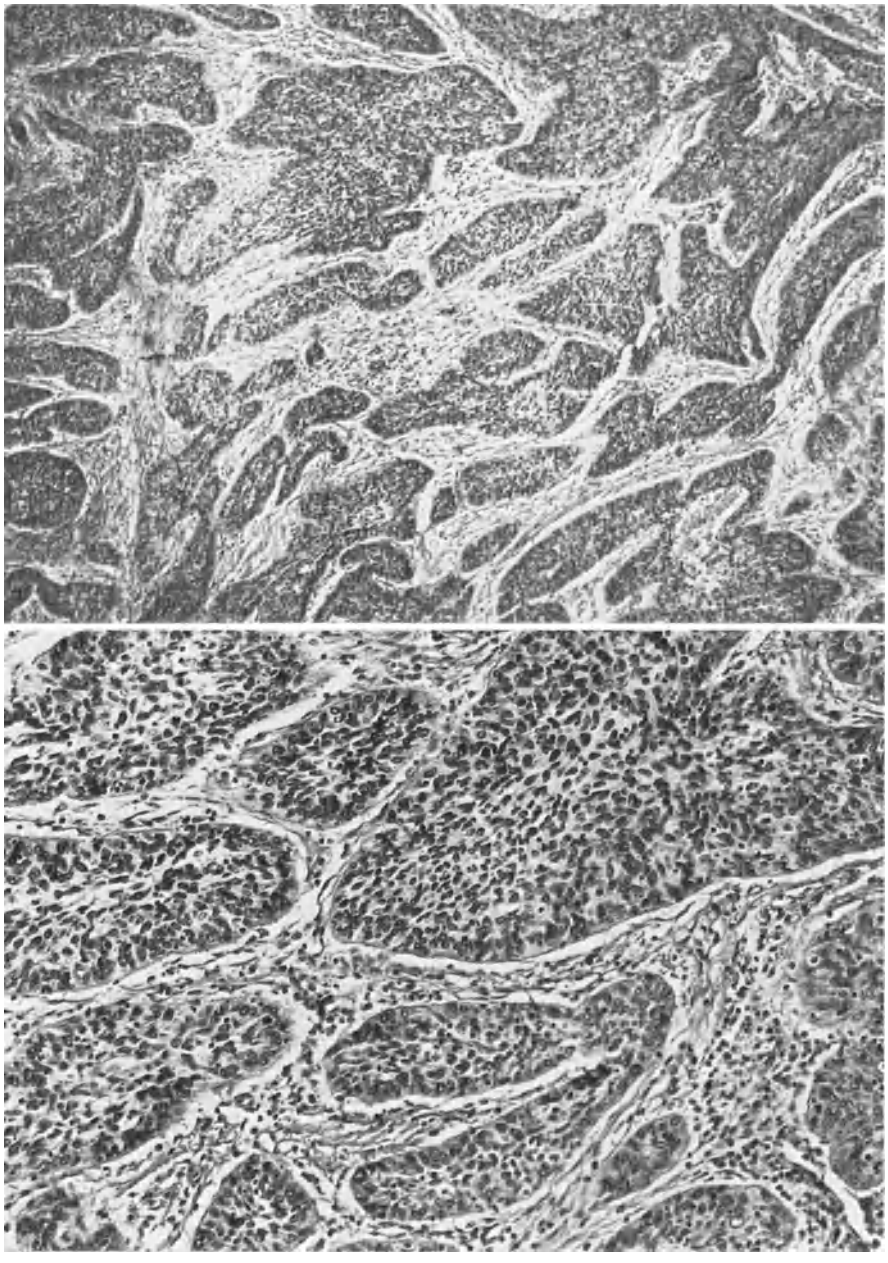

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Fig. 17a, b. Nonkeratinizing squamous cell carcinoma of the cervix. H & E: **a** × 60; **b** × 150;

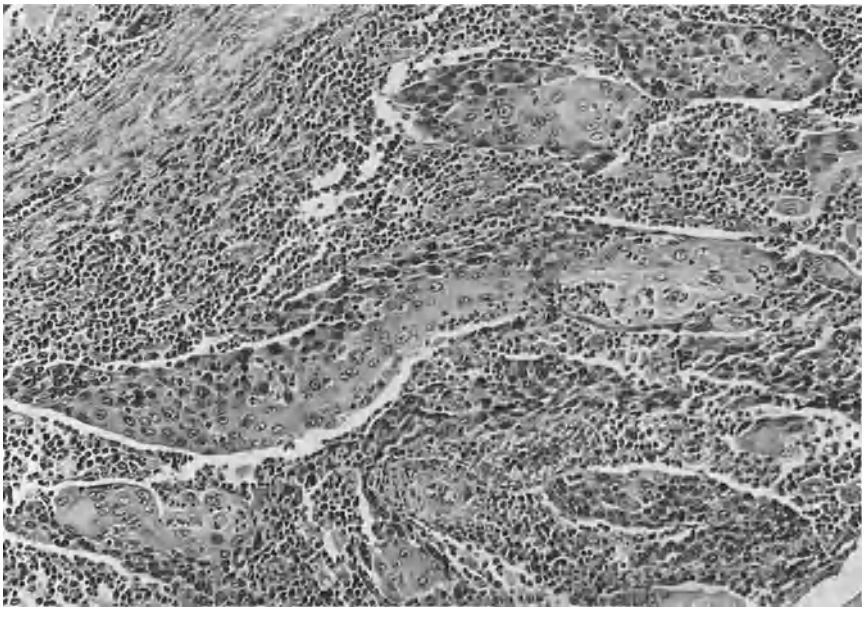

Fig. 18. Keratinizing squamous cell carcinoma in a patient who had taken oral contraceptives for many years. H & E, × 150

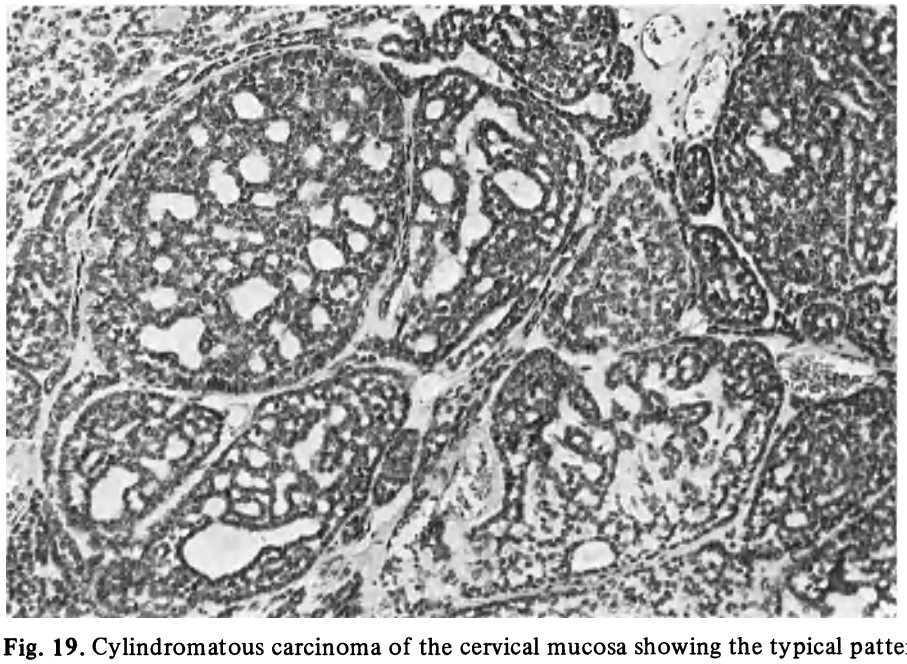

Fig. 19. Cylindromatous carcinoma of the cervical mucosa showing the typical pattern. H & E, × 150

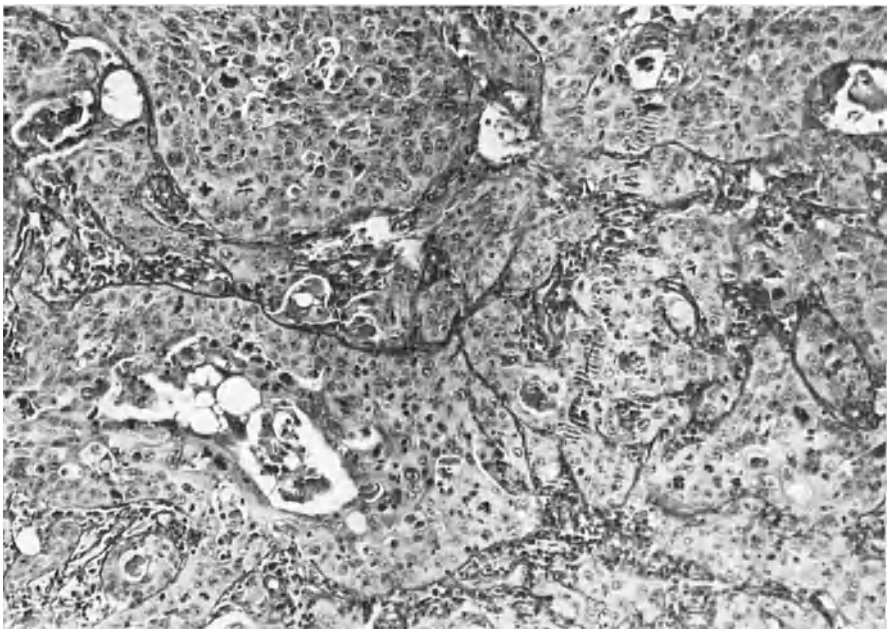

Fig. 20. Mucoepidermoid carcinoma of the cervical mucosa in a patient who had taken an oral contraceptive containing Norgestrel for 8 years. Single-cell mucoid change and small mucous cysts in the vicinity of the squamous epithelium; also single-cell keratinization. H & E, × 150

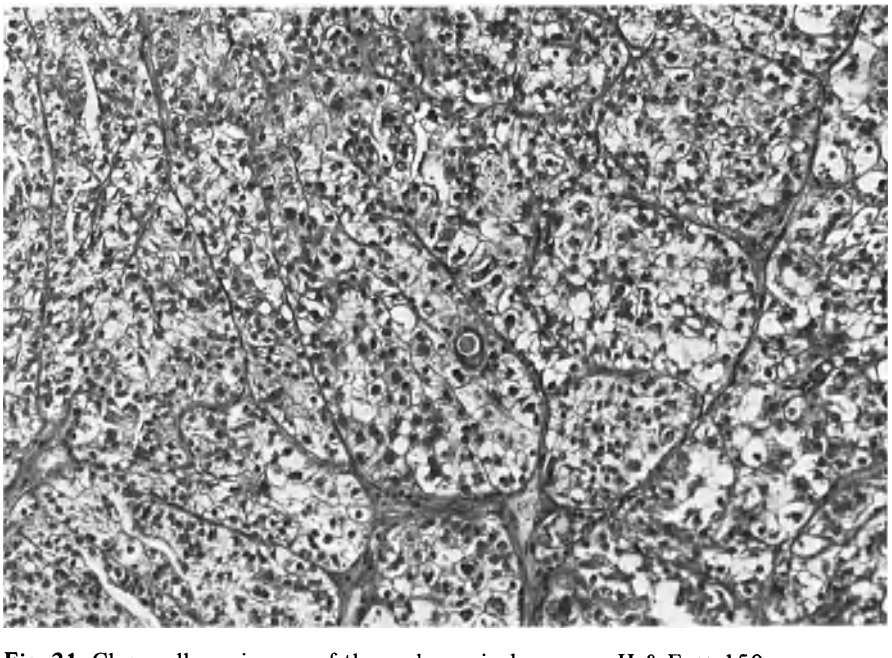

Fig. 21. Clear-cell carcinoma of the endocervical mucosa. H & E, × 150

should also be classified under this heading as variants – perhaps even less mature – of mucoepidermoid carcinoma (Fig. 21).

As a result of many years' study of women taking hormones, it has become apparent that intraepithelial neoplasias derived from stratified squamous epithelium predominate among those who have received high-estrogen products, whereas neoplasias derived from reserve cells predominate among patients who have taken high-progestogen formulations (Table 2). This fact is not enough to prove a causal association between hormone treatment and the development of preneoplastic lesions, but statistical analysis of a large series has revealed an increased incidence of preneoplastic lesions among women on oral contraceptives, as well as a shift towards the younger age groups (Table 3).

The development of these precursor lesions must, however, still be regarded as multifactorial, commencement of intercourse at an earlier stage in life, frequent change of partners, and chronic irritation from persistent inflammation being among the causative influences. In this connection there is one striking and remarkable observation, namely, that in a certain category of young girls, admittedly not numerous, who have taken ovulation inhibitors for the treatment of skin disease and who, being demonstrably virgins, have never had intercourse, the incidence of preneoplastic lesions is higher than normal, with the lesions tending to occur earlier in life than would normally be expected.

Yet another problem is the possible etiologic role of hormones in *adenocarcinoma of the endocervical mucosa,* formerly a very rare cancer, but now becoming more common. The precursors of this type of carcinoma are atypical adenomatous hyperplasia and adenocarcinoma in situ of the endocervical mucosa. *Adenomatous hyperplasia* was at one time compared, albeit somewhat uncritically, with the physiologic hyperplasia of the endocervical mucosa which occurs in pregnancy, but it is clearly distinguished from the latter by its compartmentalization into microalveolar spaces, with reserve cell hyperplasia and extensive replacement of the stroma, together with a state of adenomatous proliferation accompanied by formation of new glands and loss of cytoplasmic differentiation (Fig. 22) (see *Dallenbach-Hellweg* 1972).

Since this novel observation was rarely made before the era of oral contraceptives, its significance remained for some time obscure. In the author's series the incidence of adenomatous hyperplasia of the cervical mucosa among women taking high-progestogen ovulation inhibitors or pure progestogen formulations is up to four times as high as in women not receiving hormones, and the association is statistically significant. A definite correlation between this type of hyperplasia or actual *adenocarcinoma in situ* (Fig. 23) and the intake of ovulation inhibitors has also been found by many other workers (*Maqueo* et al. 1966; *Lauchlan* and *Penner* 1967; *Taylor* et al. 1967; *Candy* and *Abell* 1968; *Kyriakos* et al. 1968; *Gall* et al. 1968; *Talbert* and *Sherry* 1969; *Nichols* and *Fidler* 1971; *Mingeot* and *Fierez* 1974; *Werner* and *Dinges* 1976). Between 80% and 100% of the women with this type of hyperplasia of the endocervical mucosa proved to have been taking oral contraceptives. As these forms of hyperplasia frequently cause vaginal discharge which does not respond to ordinary measures, such patients are often treated by performing a cone biopsy of the cervix and are thus lost to subsequent cytologic follow-up. Furthermore, because of vaginal discharge, patients are often reluctant to continue taking an oral contraceptive; that reluctance is one of the

Table 2. Incidence of abnormalities in the cervix in patients receiving estrogen (E), progestogens (P), or no hormones, broken down by age groups. All figures are percentages

	26–35 years			36–45 years			46–55 years			Over 55 years		
	E	P	None	E	P	None	E	P	None	E	P	None
Squamous cell metaplasia	0	19	24	19	30	21	29	23	20	28	17	14
Cystic hyperplasia	0	4	8	22	14	14	12	16	21	10	17	13
Adenomatous hyperplasia	0	19	16	19	27	15	13	22	11	7	8	6
Inflammatory erosion	25	65	65	66	57	62	52	45	55	48	33	36
Dysplasia, squamous type	25	19	12	3	17	8	7	7	7	5	8	6
Carcinoma in situ, squamous type	0	4	3	6	2	2	2	0	2	1	0	2
Dysplasia, reserve cell type	0	4	1	0	3	0	1	1	1	0	0	1
Carcinoma in situ, reserve cell type	0	4	1	0	0	1	1	0	1	0	0	1
Squamous cell carcinoma	0		1	0		0	1		2	2		9
Adenocarcinoma	0		0	0		1	1		0	1		3
Parakeratosis, Leukoplakia	50	42	37	44	29	38	36	30	24	44	8	27

Table 3. Incidence of abnormalities in the cervix in patients taking or not taking oral contraceptives, broken down by age groups. All figures are percentages

	16–25 years		26–35 years		36–45 years		45–65 years	
	Taking oral contra-ceptives	Not taking oral contra-ceptives	Taking oral contra-ceptives	Not taking oral contra-ceptives	Taking oral contrap ceptives	Not taking oral contra-ceptives	Taking oral contra-ceptives	Not taking oral contra-ceptives
Squamous metaplasia	39	27	29	24	29	21	31	20
Cystic hyperplasia	1	4	6	8	14	14	14	21
Adenomatous hyperplasia	67	21	56	16	47	15	31	11
Reserve cell hyperplasia	28	15	27	13	24	12	21	15
Inflammatory erosion	87	80	75	65	72	62	63	55
Papillomatosis	4	1	2	1	1	0	0	0
Dysplasia	33	20	24	13	17	8	12	7
Carcinoma in situ	7	6	9	4	5	3	4	2
Squamous cell carcinoma Adenocarcinoma	2	0	2	1	3	2	3	2

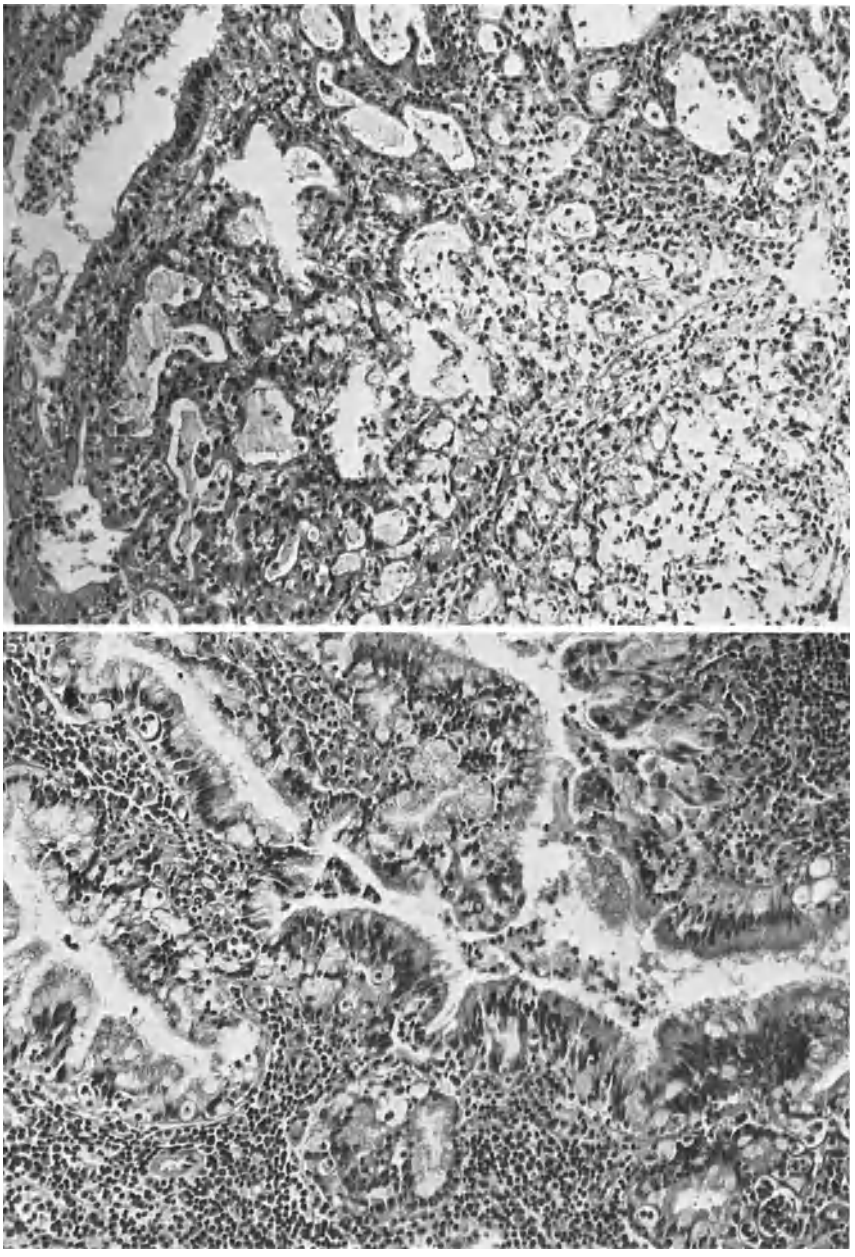

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Fig. 22a, b. Adenomatous hyperplasia of the endocervical mucosa in a woman who had taken an oral contraceptive containing Norgestrel for 9 years. **a** Microalveolar gland pattern with partial or complete disappearance of the stroma. **b** Adenomatous proliferations with poor differentiation of the covering epithelium and conspicuous epithelial proliferation with formation of intraluminal epithelial papillae. H & E, × 150 (**a** and **b**)

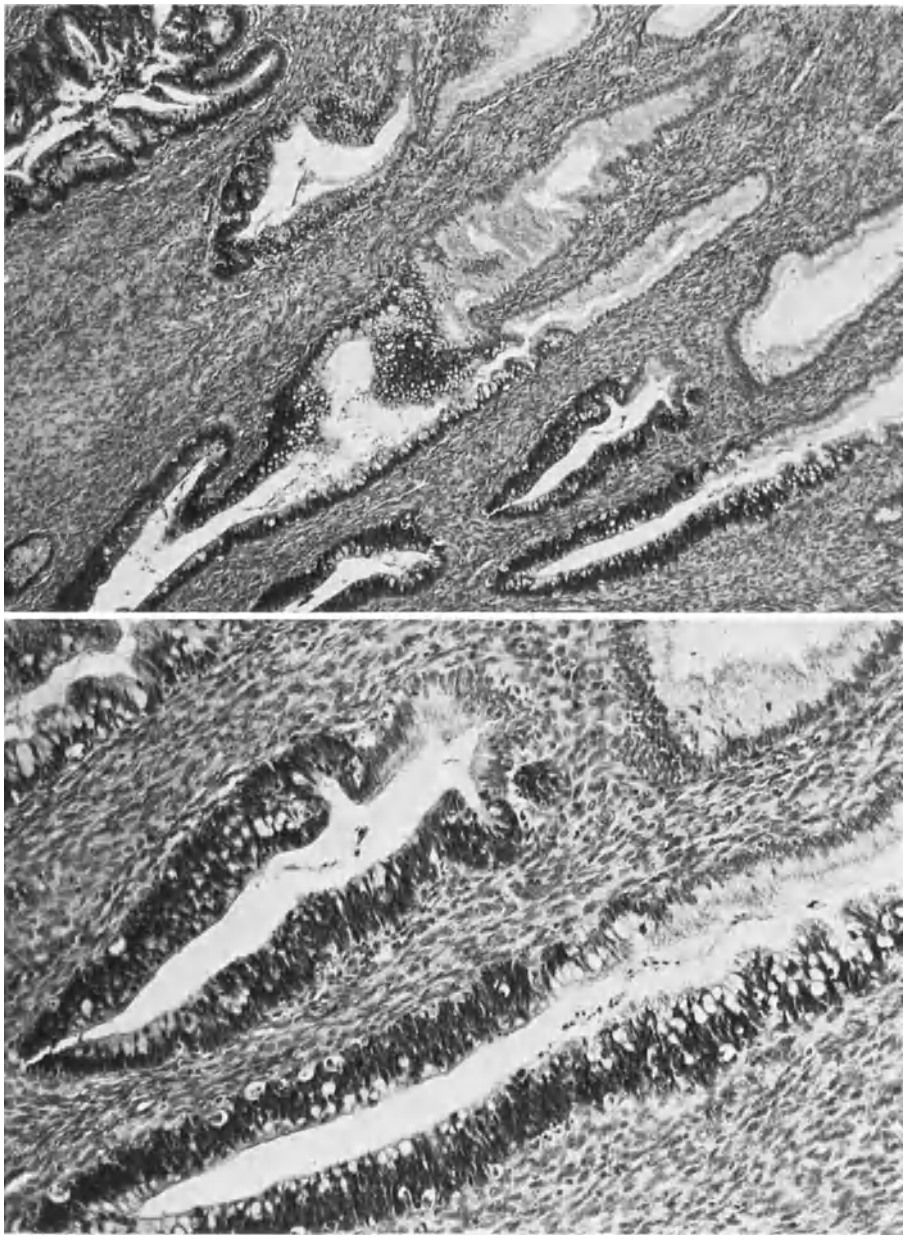

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Fig. 23a, b. Adenocarcinoma in situ of the endocervical mucosa in a woman who had taken an oral contraceptive containing Norgestrel for many years. Extreme nuclear immaturity. The abnormal glandular epithelium shows multiple layers or rows of cells and is sharply demarcated from the as yet normal glandular epithelium. Within the atypical epithelium there are intraluminal epithelial papillae and, just commencing, areas of microalveolar pattern. H & E, × 60 (**a** and **b**)

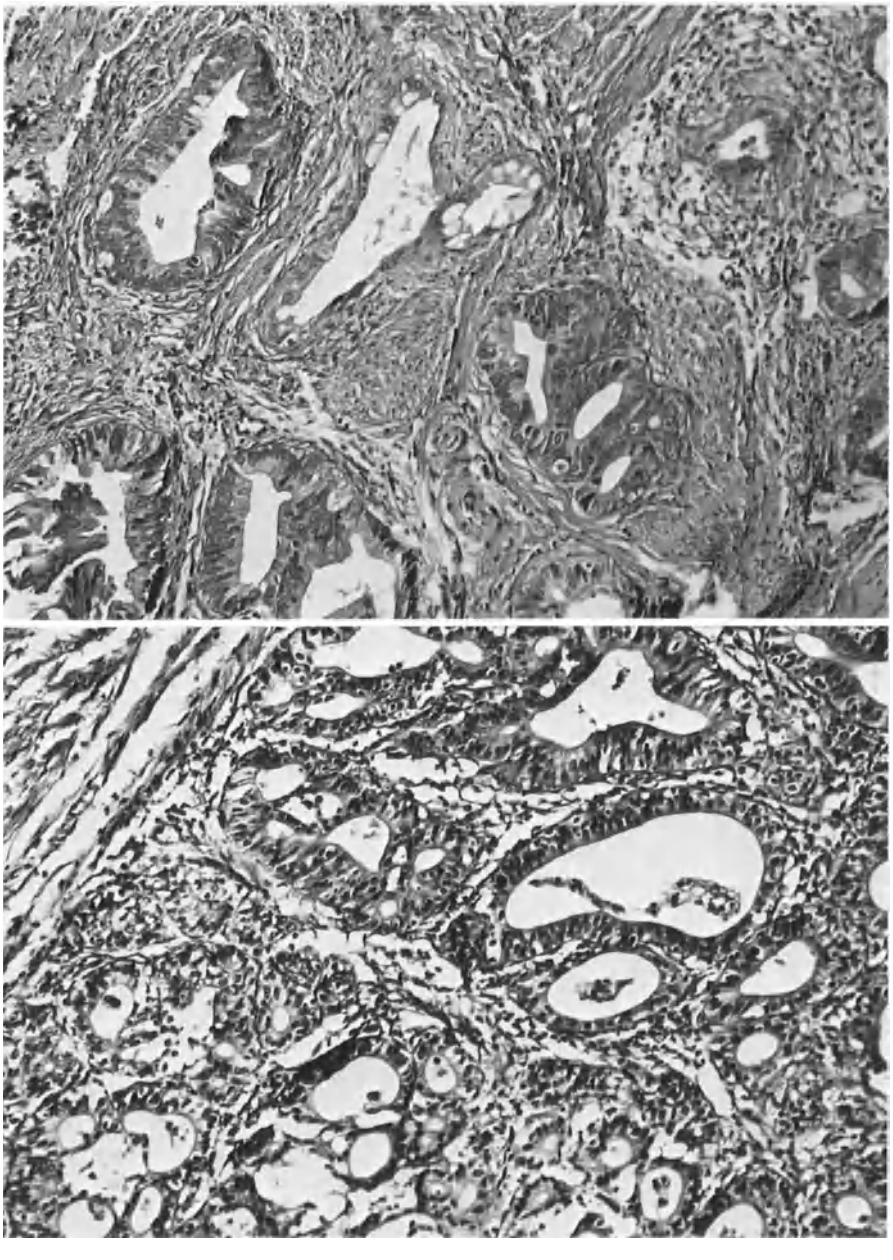

Fig. 24a, b. Adenocarcinoma of the endocervical mucosa in a woman who had taken oral contraceptives containing Norgestrel for many years. **a** Predominantly adenomatous proliferation of the carcinomatous glands with infiltration extending as far as the outer wall of the cervix. **b** In addition to adenomatous proliferation, the carcinomatous glandular epithelium also shows a microalveolar pattern together with increasing immaturity. H & E, × 150 (**a** and **b**)

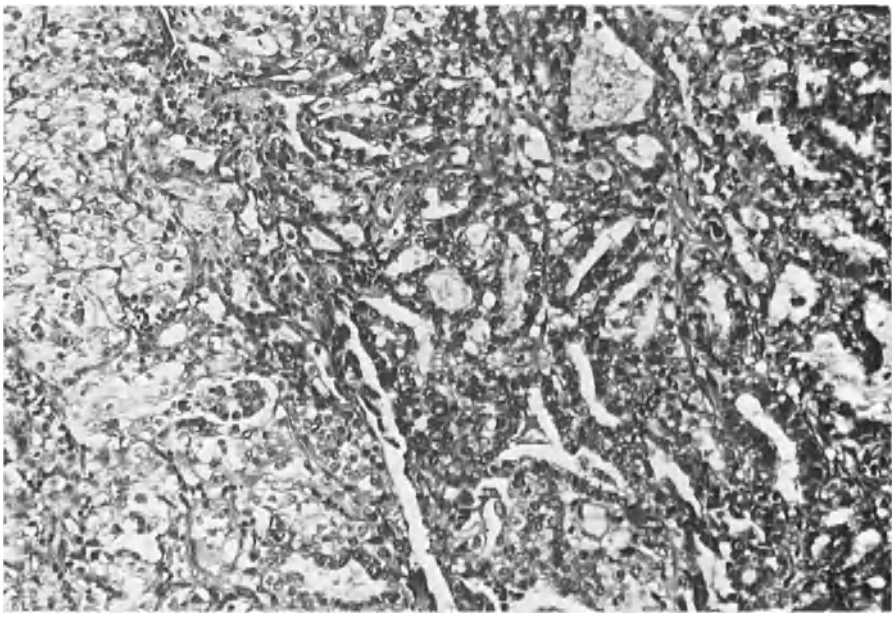

Fig. 25. An extremely immature adenocarcinoma of the endocervical mucosa. Microalveolar pattern with little or no differentiation. The stroma has completely disappeared and there is wide ranging infiltration of the cervical wall. H & E, x 150

reasons which influences the gynecologist in advocating hysterectomy for women who do not wish to have any more children.

Nevertheless, in our own research there is an increasing incidence of *adenocarcinoma of the endocervical mucosa* among women who have been on a high-progestogen contraceptive for an average of 10 years. This observation is supported by published reports (*Ky* et al. 1974; *Qizilbash* 1975: four patients; *Gallup* and *Abel* 1977: five patients under 32 years; *Czernobilski* et al. 1974). In histologic structure these carcinomas show clear evidence of having originated from atypical adenomatous hyperplasia (Figs. 24 and 25). In addition to adenomatous proliferations with the appearance of adenocarcinoma in situ and infiltrating the cervical wall, there are areas of densely packed microalveolar patterns with remnants of surrounding mucoid-dysplastic epithelium.

The observation that an invasive adenocarcinoma of the endocervical mucosa may be preceded by in situ changes of many years' duration is not new (*Friedell* and *McKay* 1953; *Burghardt* 1966; *Krimmenau* 1966) and has been confirmed by more recent reports, some from patients on oral contraceptives and others from patients who had not taken them (*Sachs* and *Würthner* 1972; *Weisbrot* et al. 1972; *Büttner* and *Kyank* 1973; *Boddington* et al. 1976; *Christopherson* et al. 1979). These workers describe and illustrate every conceivable form of transition of atypical adenomatous gland proliferation and immature reserve cell hyperplasia. In the last few years there has been a sharp rise in the percentage of adenocarcinomas among the total of cases of carcinoma of the cervix: from 3.4% (*Carter* et al. 1949) and 5% (*Abell* and *Gosling*

1962) to 9.6% (*Gallup* and *Abell* 1977), whereas before the era of oral contraceptives, adenocarcinoma of the endocervical mucosa was almost entirely confined to elderly women. In their series of cervical carcinoma, *Davis* and *Moon* (1975) found 34% were adenocarcinomas.

Though we are still in new and unexplored territory, there seem to be valid grounds for suspecting an etiologic link between progestogen administration and this type of carcinoma. The evidence is at least sufficient to call for a vigorous research effort. From the writer's observations, it appears that of all the miscellaneous progestogen products the one most closely implicated in these atypical hyperplasias and carcinomas is the highly potent hormone norgestrel. All our patients with adenocarcinoma in situ or invasive carcinoma of the endocervix had taken ovulation inhibitors containing norgestrel.

In conclusion, it seems reasonable to state that hormone products influence the processes of regeneration and preneoplastic transformation which occur during the re-epithelialization of cervical erosions. The hormones apparently exert their effects by means of specific proliferation stimuli directed at one or another of the types of epithelium participating in these reepithelialization phenomena. There seems to be no direct etiologic connection between hormone administration and squamous carcinoma of the cervix; at any rate, no evidence of such a link has yet been uncovered. However, the published observations strongly suggest that there is an association between hormone administration and adenocarcinoma of the endocervical mucosa.

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Precursors of Cervical Cancer: Ultrastructural Morphology

H.-E. STEGNER

A. Introduction

Under normal conditions the cervix is covered by three types of epithelium: original squamous, original columnar, and metaplastic. While both the squamous and columnar epithelia, despite hormone-dependent changes, maintain their typical basic structure throughout life, metaplasia of the squamocolumnar junction exhibits a great variety of structural patterns. The great majority of neoplastic disorders of the uterine cervix apparently arise from a primarily disturbed squamous metaplasia. On the other hand, mature (consolidated) squamous metaplasia, once established, may decrease the risk of malignant neoplasia in that area. The basic cell population of squamous metaplasia is composed of poorly differentiated subcolumnar reserve cells. The genesis of reserve cells is still a matter of controversy, although the theory that they originate from cervical glandular cells is widely accepted. Reserve cells are primitive cells of bivalent differentiation capacity. One vector of differentiation leads to the development of mucus-secreting gland cells, the other to stratified squamous epithelium. Mature squamous metaplasia is referred to as "epidermization," "complete metaplasia," or "consolidated metaplasia."

Both the mucogenetic and keratogenetic potentials of primitive reserve cells can be more or less realized in the various types of precancerous lesions of the cervix. Although a wide range of mucoepidermal or keratinizing differentiation is well known in invasive cervical cancer, corresponding distinctions have not been adopted in the current classification of carcinoma in situ. This has led to considerable misunderstanding in the definition and interpretation of the precursor lesions of cervical cancer. More than conventional histologic methods, ultrastructural analysis has revealed in atypical epithelia a great spectrum of structural patterns, which can only be understood on the basis of normal epithelial differentiation. The ultrastructural findings in atypical epithelia have engendered further arguments for a new classification of precancerous lesions of the uterine cervix.

B. Ultrastructure of Normal Cervical Epithelia

The fine structures of normal cervical epithelia have been described by a number of researchers (*Berger* et al. 1958; *Glatthaar* and *Vogel* 1958; *Philipp* and *Overbeck* 1959; *Ashworth* et al. 1961; *Moricard* and *Cartier* 1964; *Bonilla-Musoles* 1969; *Stegner* and *Pape* 1973; *Jordan* 1976; *Shingleton* and *Lawrence* 1976).

The *squamous epithelium* is separated from the stroma by an undulating basement membrane, measuring 400–500 Å in thickness. The basal cells show semidesmosomes in relation to the basement membrane (Fig. 1). Basal squamous cells have a high

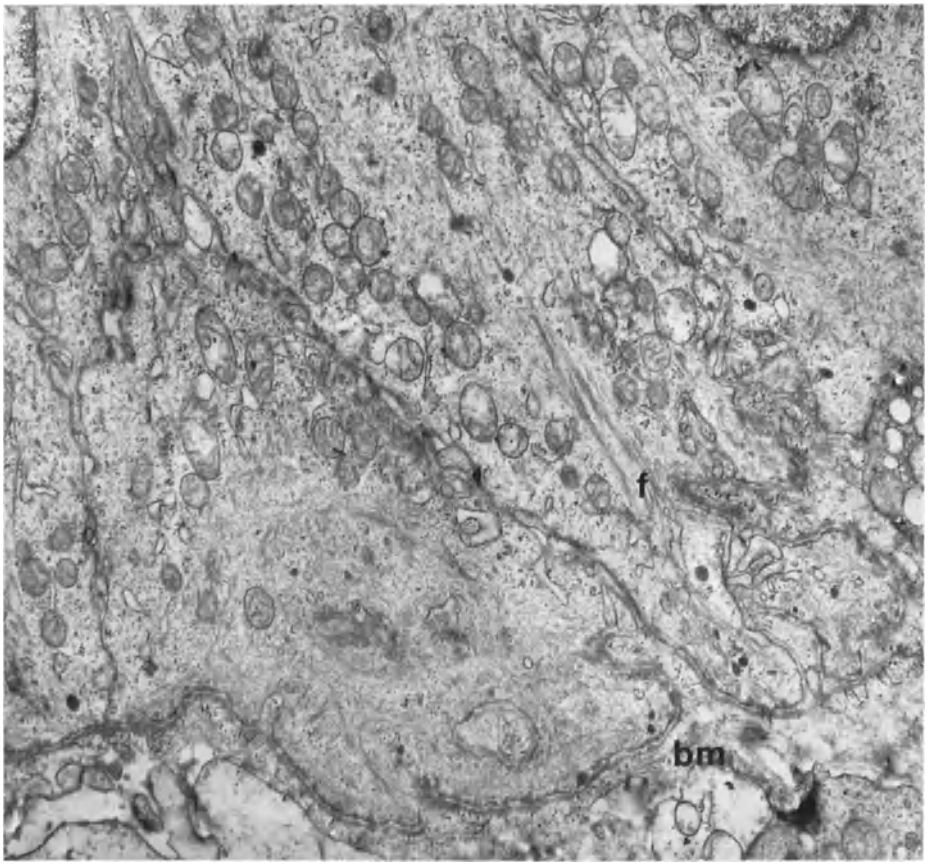


Fig. 1. Basal cell layer of normal squamous epithelium. *bm,* basement membrane with numerous half desmosomes; *f,* intracytoplasmic fibrils. x 19 800

nucleocytoplasmic ratio. Their nuclei are oval or elongated, their chromatin, finely granular (Fig. 2). Heterochromatin is peripherally located. A single round nucleolus is usually present. The cytoplasm contains ribosomes, mitochondria, small amounts of granular endoplasmic reticulum, Golgi structures, and tonofilaments, which measure approximately 70 Å in diameter and course throughout the cytoplasm or surround the

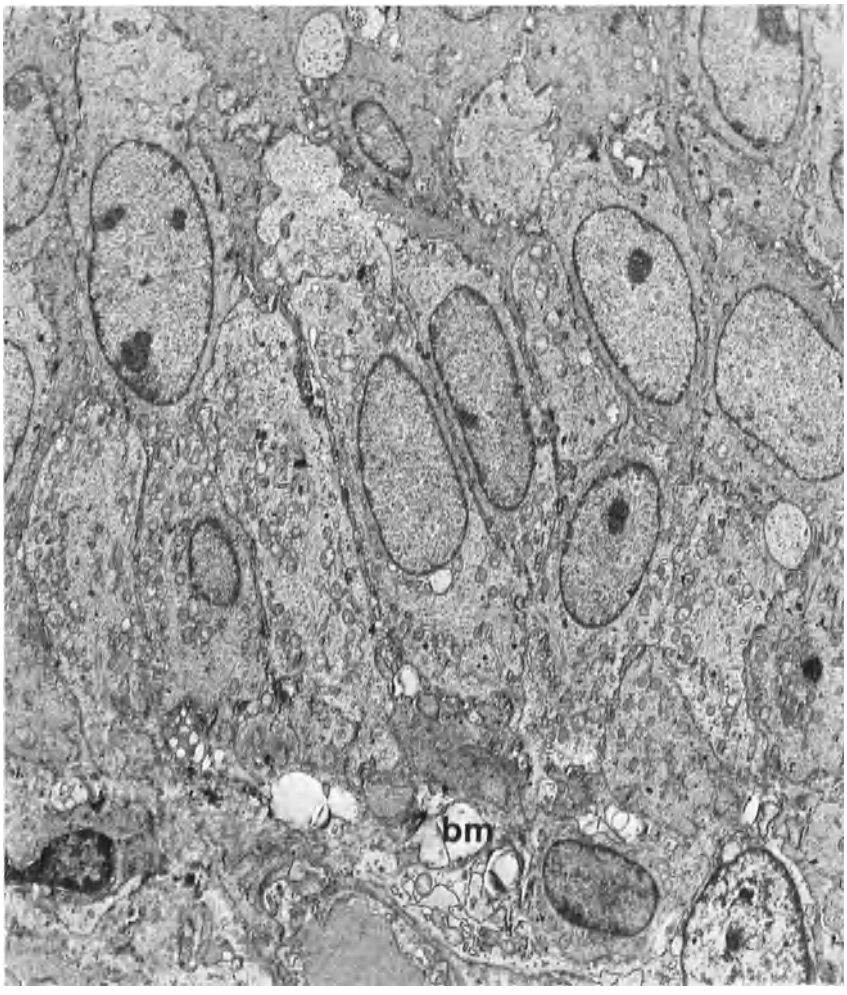


Fig. 2. Basal and parabasal cell layer of normal cervical squamous epithelium. Nuclei of basal cells are oval shaped, chromatin is finely granular. *bm,* basement membrane. × 6600

nucleus. During mitosis the basal cell is shifted above the level of the monocellular basal layer, but remains in contact with the basement membrane by way of slender cytoplasmic projections (Fig. 3). These findings indicate that mitotic activity is predominantly confined to basal cells, not to parabasal cells as was commonly assumed from conventional light microscope studies of ^{3}H-thymidine labeled tissue sections.

Adjacent basal cells are separated by an intercellular space of variable width, into which small microvilli project. As the cells mature, their nuclei become smaller and their cytoplasm, more flattened. Their ribosomes decrease, but the tonofibrils increase, terminating on the inner surface of the attachment plaques of the desmosomes. In the intermediate zone of the epithelium the cells are in close contact (Fig. 4). Large areas of the cytoplasm are occupied by aggregates of glycogen granules (Fig. 5). Desmosomes

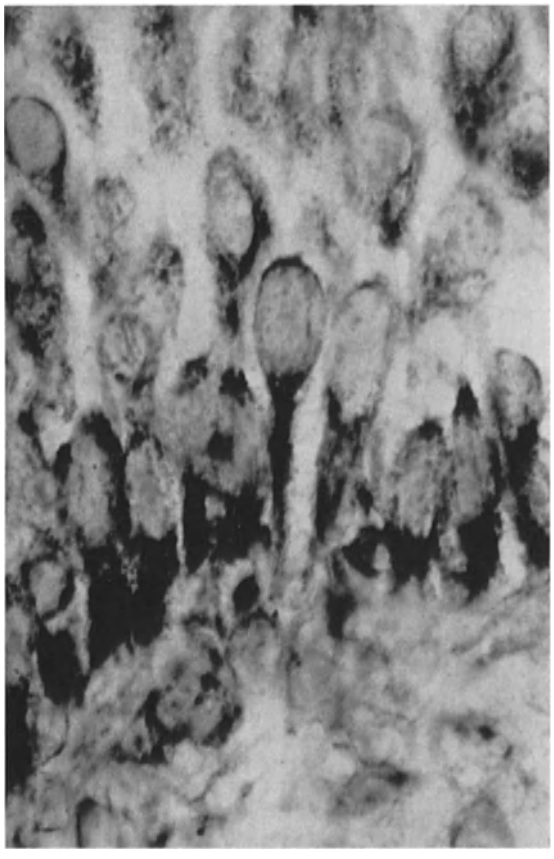


Fig. 3. Large basal cells obviously in the phase of premitotic DNA reduplication. The cells are shifted above the level of the basal cell layer but are still in contact with basement membrane through slender cytoplasmic protrusions

are well developed, and tonofibrils are numerous (Fig. 6). In the upper third of the epithelium the cells are flattened onto a plane parallel to the surface. The nuclear chromatin is condensed, and the outer membrane of the nuclear envelope has frequently disappeared. As metabolism wanes, the cytoplasm becomes poor in organelles, containing only a few degenerating mitochondria, some glycogen granules, and tonofibrils. The desmosomes are small, and cell interconnections are less intensely formed, thus favoring spontaneous cell desquamation (Fig. 7). As observed by scanning electron microscopy (SEM), the squamous epithelium reveals a smooth surface (*Hackeman* et al. 1968; *Shingleton* et al. 1968; *Jordan* and *Allen* 1977; *Hiersche* and *Wagner* 1978). The superficial cells are flat and polygonal with a centrally raised nuclear area and prominent terminal bars between adjacent cells. The surface of each cell has a typical pattern of microridges approximately 0.15 nm wide with spaces of about 0.25 nm in between. The fingerprint-like microridges form irregular whorling structures in the center of the cells, but peripherally they are often arranged parallel to the cell boundaries.

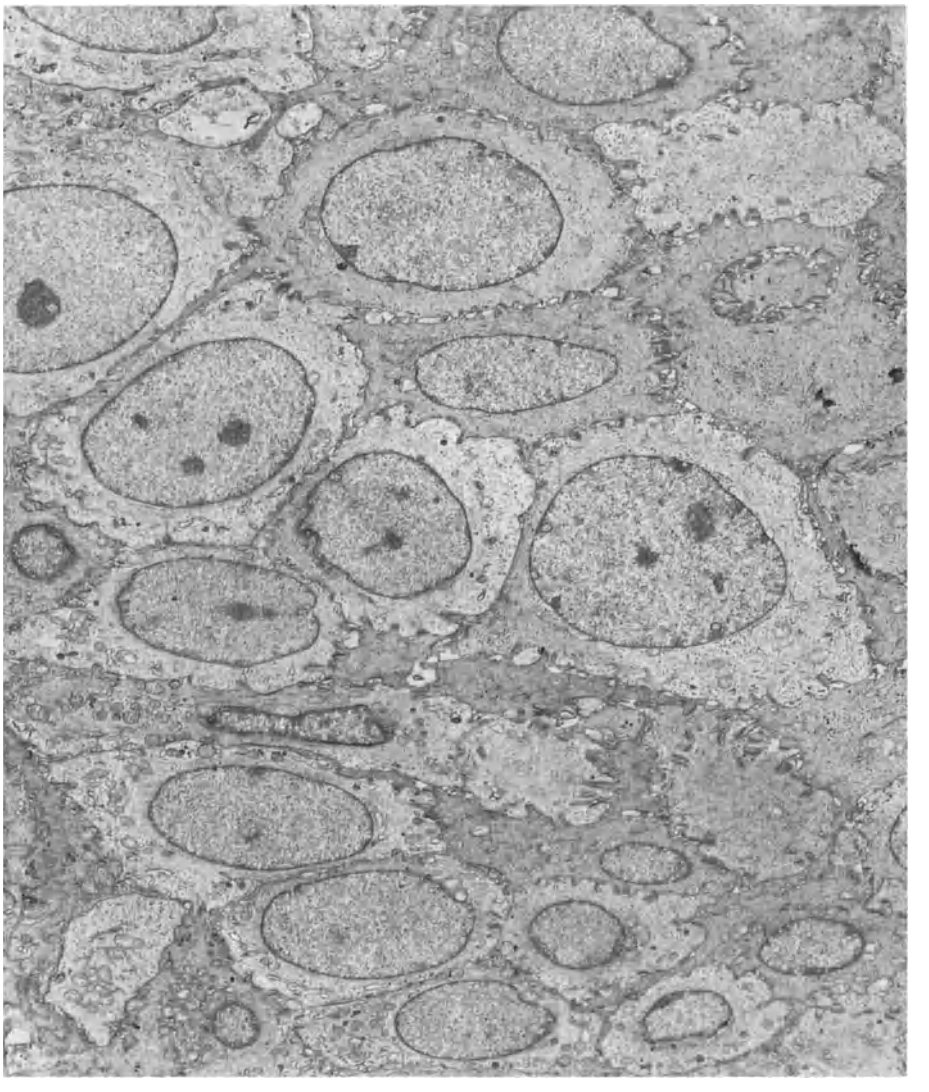


Fig. 4. Intermediate zone of normal squamous epithelium. The polyhedral cells are in close contact. Cell interconnection is established by numerous desmosomes. × 5800

The cervical *columnar epithelium* consists of a single layer of cylindrical cells. Their nuclei are located basally and are round or oval, but may be convoluted during phases of high secretory activity of the cell. The cytoplasm is filled with secretory droplets, which contain fine, granular material of low electron density (Fig. 8) (*Hashimoto* and *Yorisato* 1959; *Gompel* 1963; *Chapman* et al. 1964; *Laguens* et al. 1967). Specific mucoproteins are synthesized within the granular reticulum and transferred to Golgi vesicles. Large, mature secretory droplets are formed by the coalescence of smaller

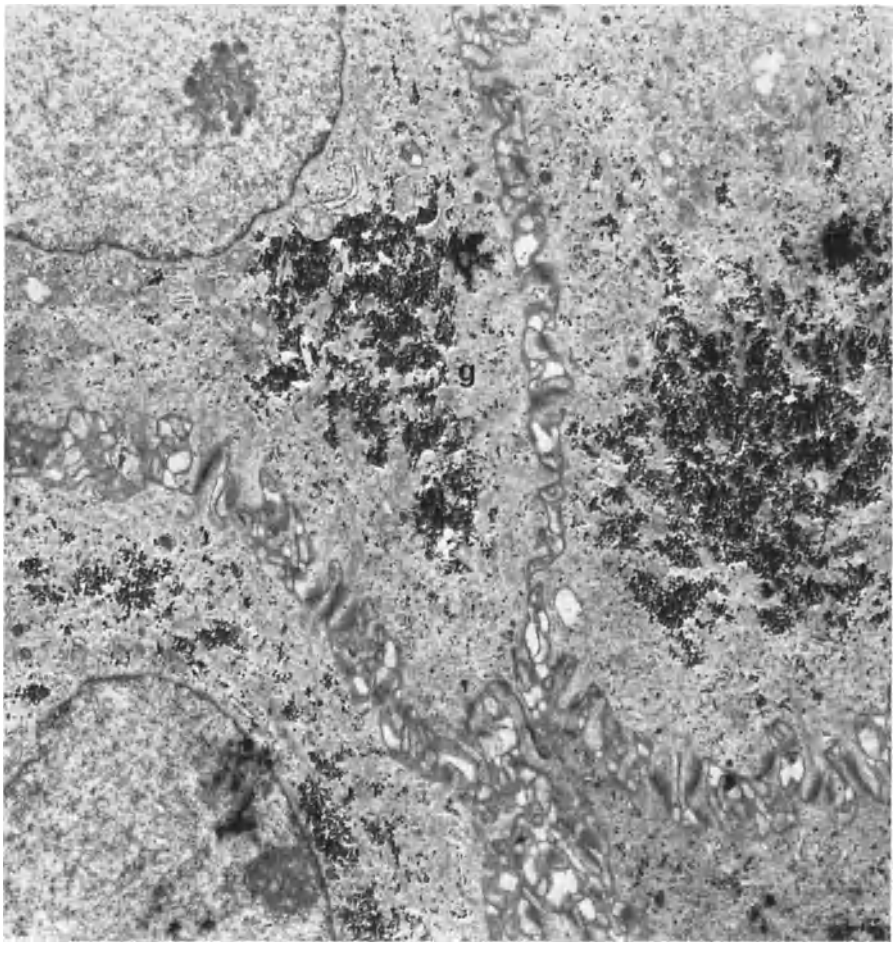


Fig. 5. Intermediate cells of normal squamous epithelium containing large aggregates of glycogen granules. × 10 000

vesicles. The droplets are extruded from the cell by either merocrine or apocrine secretion (*Philipp* 1971). At no time does a direct connection between the contents of the cell and the free lumen of the cervical gland exist. Thus the cellular control of quantity and quality of the extruded mucus is maintained. Between secretory cells, which change their fine structural morphology during various stages of functional activity, nonsecretory ciliated cells are found either in groups or singly. They are more numerous in the upper region of the endocervical canal. In surface electron microscopy the villi of cervical mucosa present a cobblestone appaearance due to closely packed columnar cells. The surface of each cell is slightly raised and covered with short microvilli. Ciliated cells are crowned by bushes of kinocilia (Fig. 9).

Squamous metaplasia describes the transformation of cervical columnar epithelium into squamous epithelium. This process is initiated by the appearance of subcolumnar

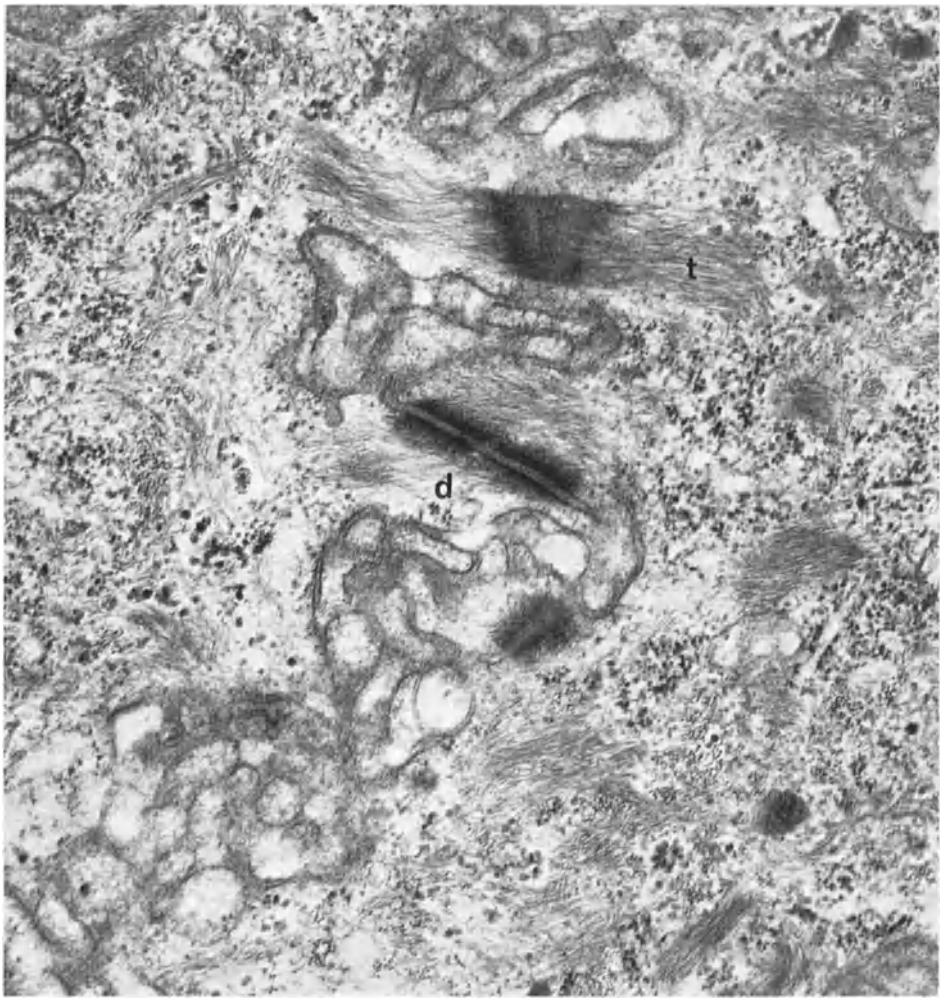


Fig. 6. High-power magnification of cell interconnections of intermediate cells. *d*, desmosomes; *t*, tonofibrils. x 42 600

reserve cells (Fig. 10). Many hypotheses have been proposed to explain the histogenesis of reserve cells. According to the theory developed by *Fluhmann* (1961), which is now widely accepted, the reserve cells are undifferentiated subcolumnar cells which originate directly from the columnar cells by unequal division and have the potential to develop into either columnar or squamous epithelium (Fig. 11). This theory is supported by the electron microscopic studies of *Song* (1964) and *Stegner* and *Beltermann* (1969). In ultrastructural analysis the cuboidal reserve cells represent the basal cell layer resting on an undulating electron microscopic basement membrane approximately 300 Å in thickness and separated from the plasma membrane by an electron lucent zone about 300 Å wide. The round nuclei are centrally located. The cyto-

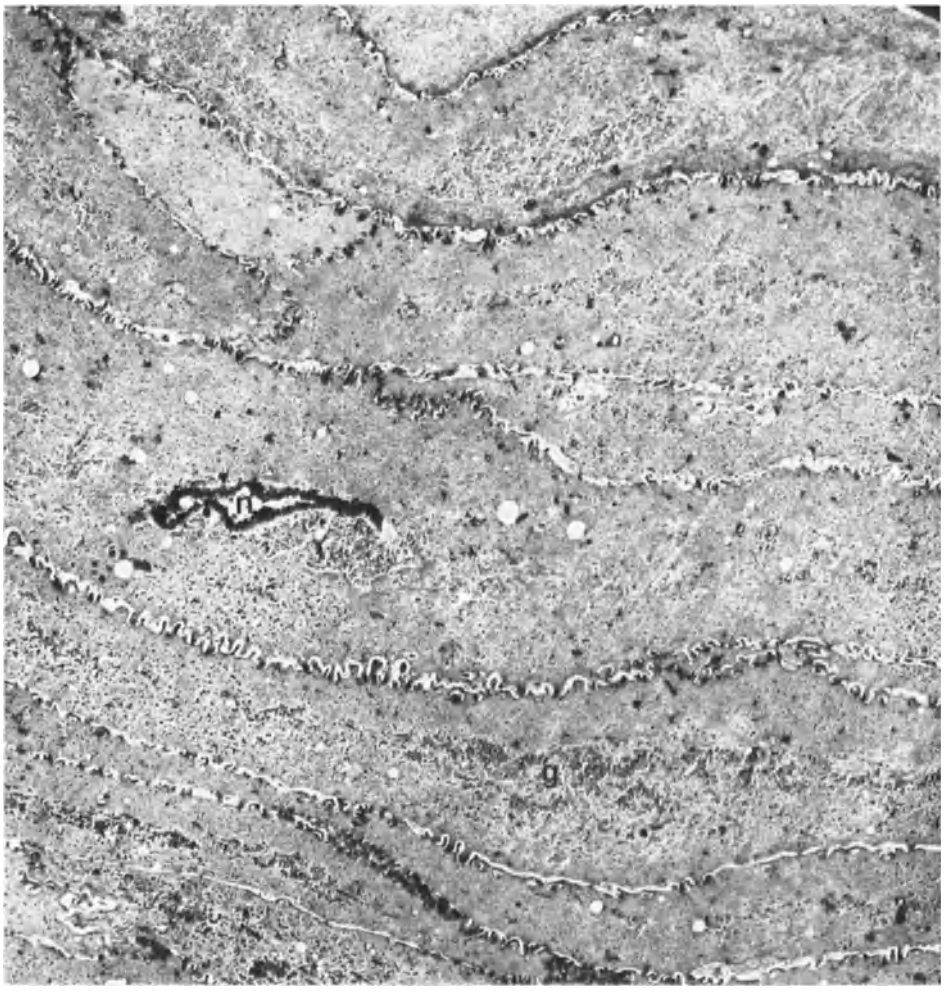


Fig. 7. Superficial cell layer of normal squamous epithelium. The cells are poor in organelles containing only small deposits of glycogen *(g)*. *n*, condensed nucleus. × 5400

plasm contains a minimum amount of organelles, indicative of the undifferentiated and prosoplastic stage of development (Fig. 12). Proliferation of reserve cells leads to the formation of several rows of cells lying between the endocervical columnar cells and the stroma. When there are more than three rows of cells, the term reserve cell hyperplasia may be used (Fig. 13). It constitutes the second step in squamous metaplasia.

In its simplest form, squamous metaplasia may be regarded as a continuation of reserve cell hyperplasia with maturation of the nuclei and differentiation of the cytoplasm. While the basal cell layer remains in an undifferentiated (basal) status, the upper layers show gradual differentiation into mature squamous cells. A conspicuous cytoplasmic feature is the occurrence of numerous bundles of tonofilaments. Although

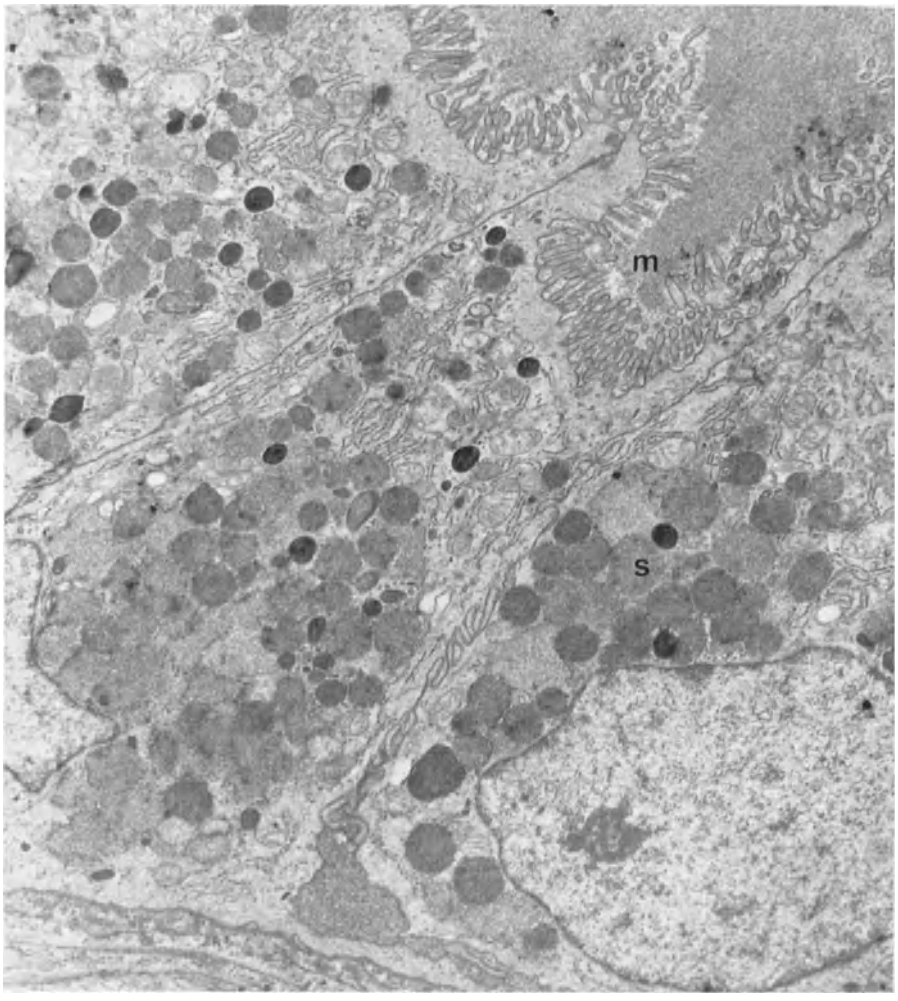


Fig. 8. Normal cervical columnar epithelium. Cytoplasm is filled by secretory droplets *(s)*, which contain finely granular material of low electron density. *m*, microvilli. × 10 000

membrane-associated ribosomes in the form of granular endoplasmic reticulum are not uncommon, free ribosomes are abundant throughout the cytoplasm. Intercellular bridges (desmosomes) are formed, and the cells acquire a polyhedral shape and become flattened in the upper layers. Glycogen deposits are rarely found in immature metaplasia (Fig. 14). Secretory cells may persist between and above the metaplastic epithelium. The original columnar cells overlying the stratified epithelium may be normal, or they may show evidence of degeneration (Fig. 15). Due to loose intercellular cohesiveness, infiltration of polymorphonuclear leucocytes and lymphocytes into immature metaplastic epithelium is facilitated.

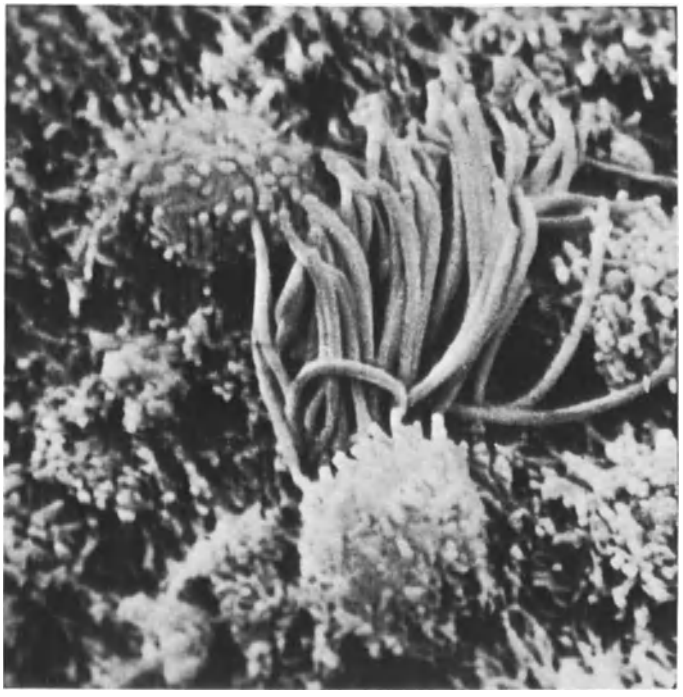


Fig. 9. Secretory and ciliated cells of cervical columnar epithelium in surface electron microscopy. (By courtesy of *H.-D. Hiersche*)

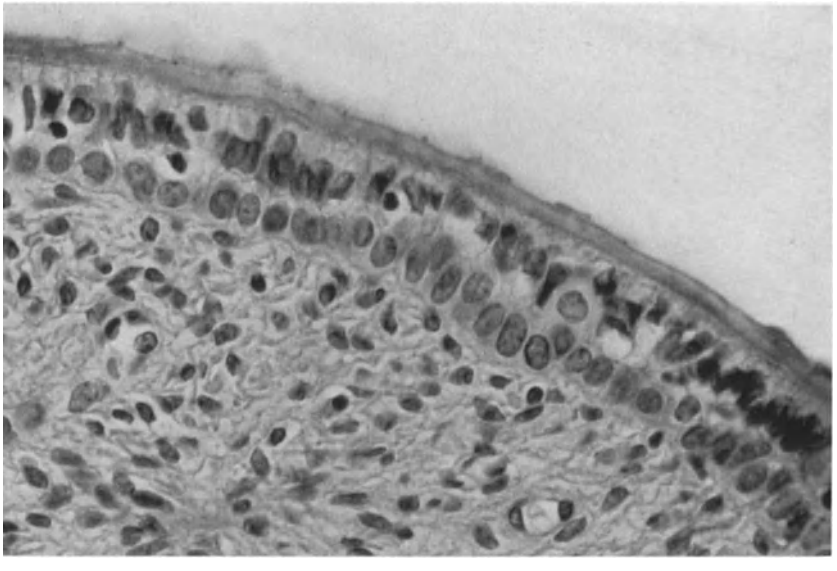


Fig. 10. Subcolumnar reserve cells of glandular epithelium

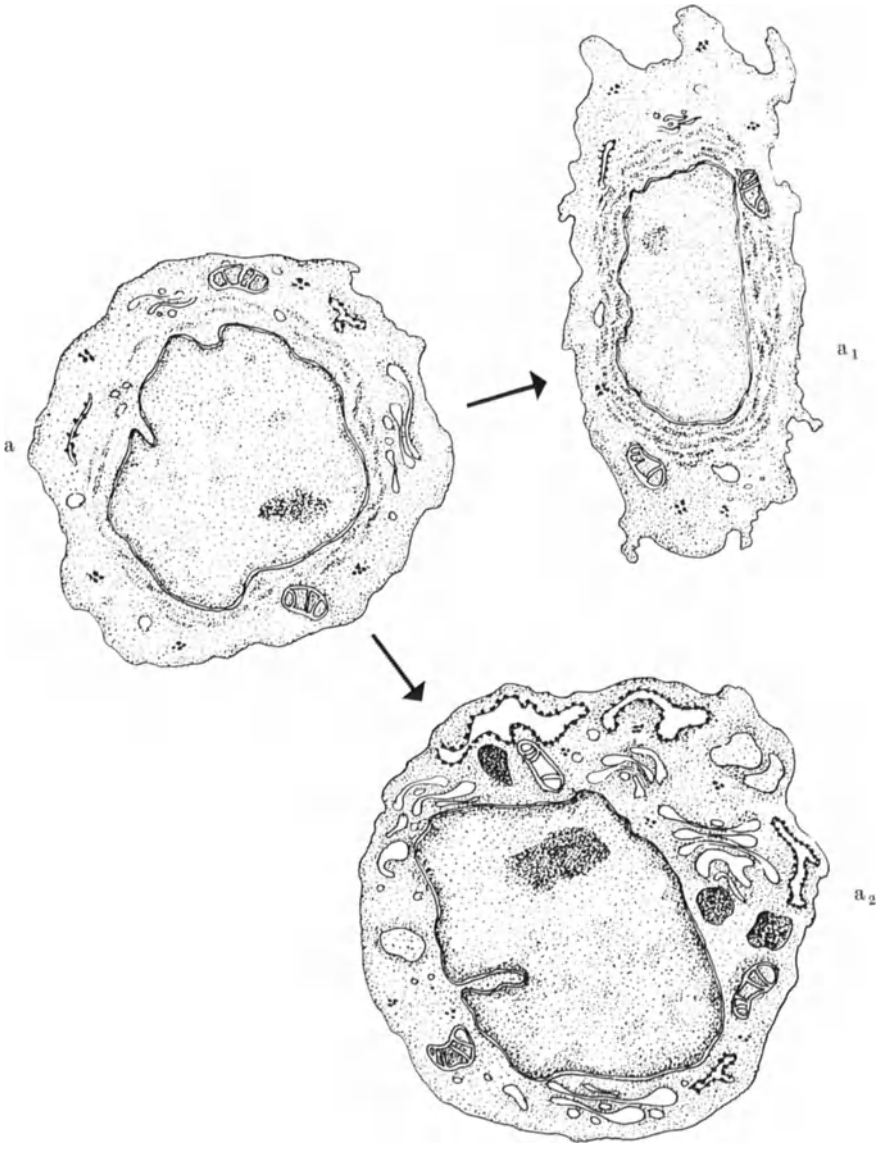


Fig. 11. Schematic drawing demonstrating bipotential differentiation of reserve cell. *Stegner* and *Beltermann* 1969

Complete squamous metaplasia exists when there is a total replacement of columnar cells by squamous epithelium. In the final stage of metaplasia, the normal strata of well-differentiated epithelium may be seen, although there may be incomplete cytoplasmic differentiation and lack of glycogen storage. Mature (complete) squamous metaplasia represents the final, non-reversible stage of epithelial transformation.

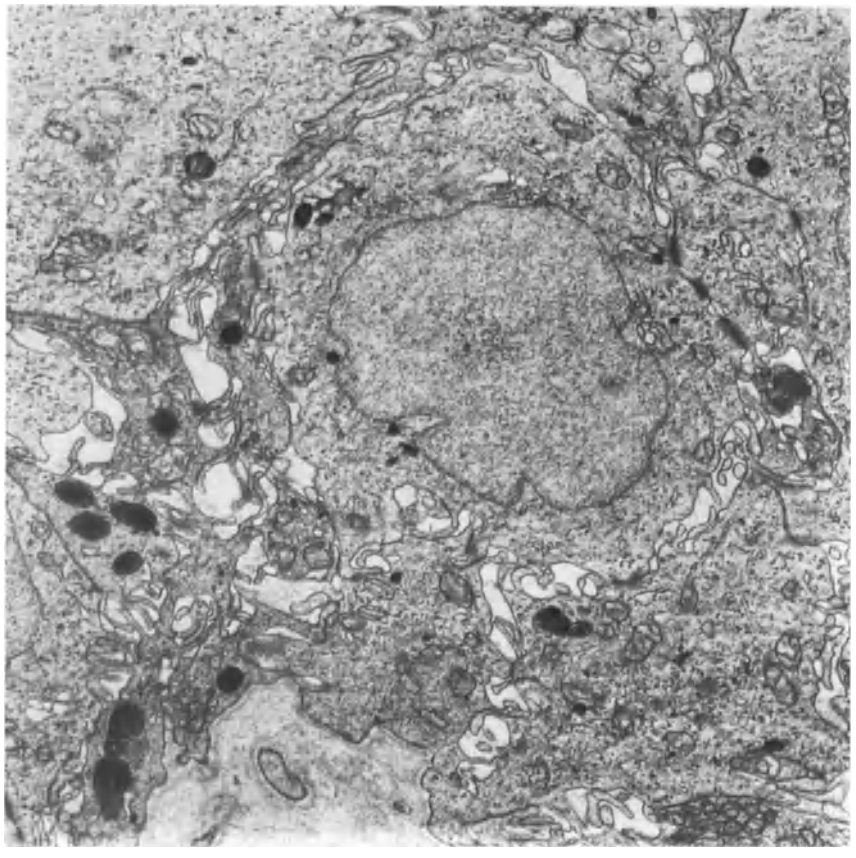


Fig. 12. Undifferentiated reserve cell. The cytoplasm contains a minimal number of organelles. *Stegner* and *Beltermann* 1969

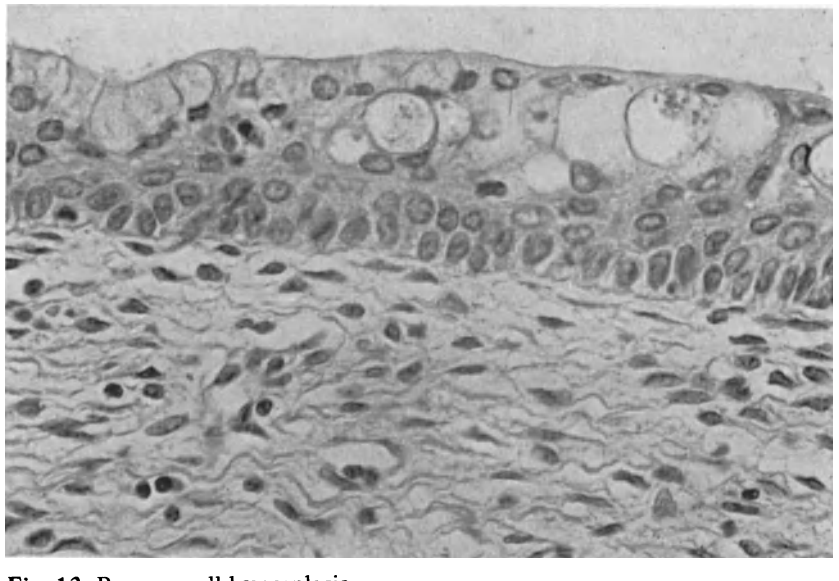


Fig. 13. Reserve cell hyperplasia

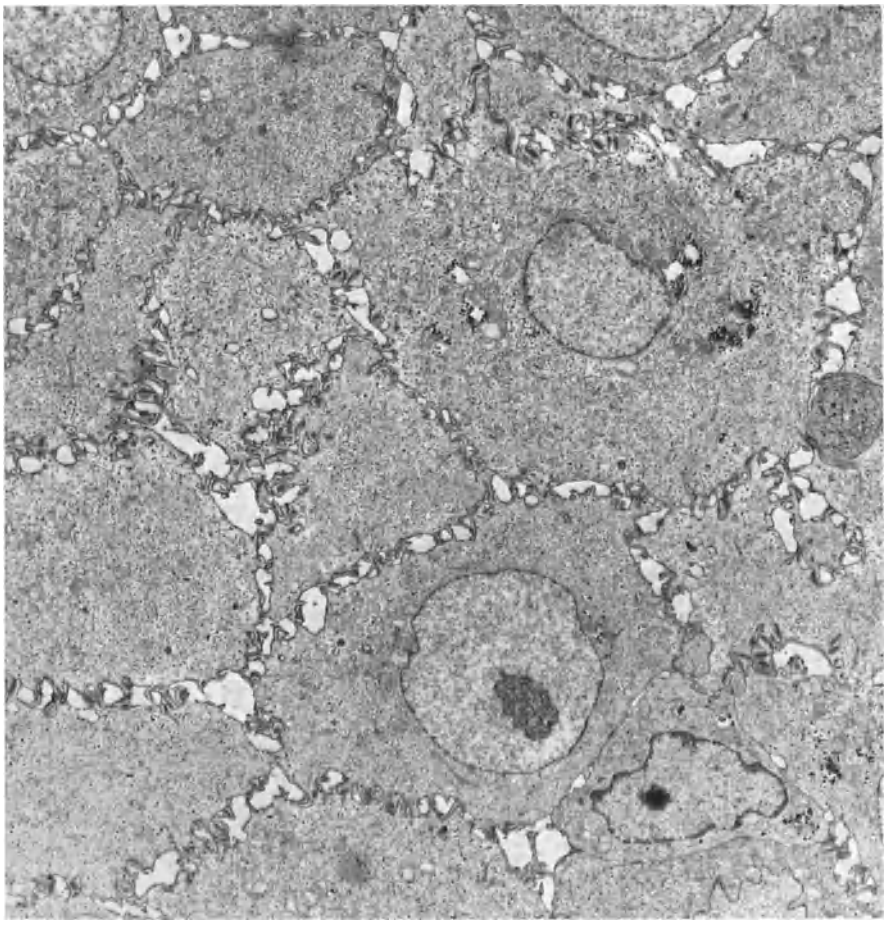


Fig. 14. Incomplete metaplasia. The metaplastic cells are polyhedral; intercellular bridges (desmosomes) are present; glycogen deposits are scarce. × 5000

C. The Concept of Dysplasia and Carcinoma in Situ

There is general agreement that invasive cervical carcinoma represents a sequeal of intraepithelial precursors which evolve slowly and may persist over a period of years until they develop into invasive and metastatic cancer. Intense study over the last 50 years revealed a great range of epithelial abnormalities which were suspected to be involved in cancer development. There were those with a relatively slight disturbance of the epithelial structure and those uniformly composed of atypical anaplastic cancer cells. Only the latter have been defined as carcinoma in situ by the International Committee on Histological Definition in 1962, thus stressing their malignant potential. All other disturbances of differentiation of squamous epithelium were classified as

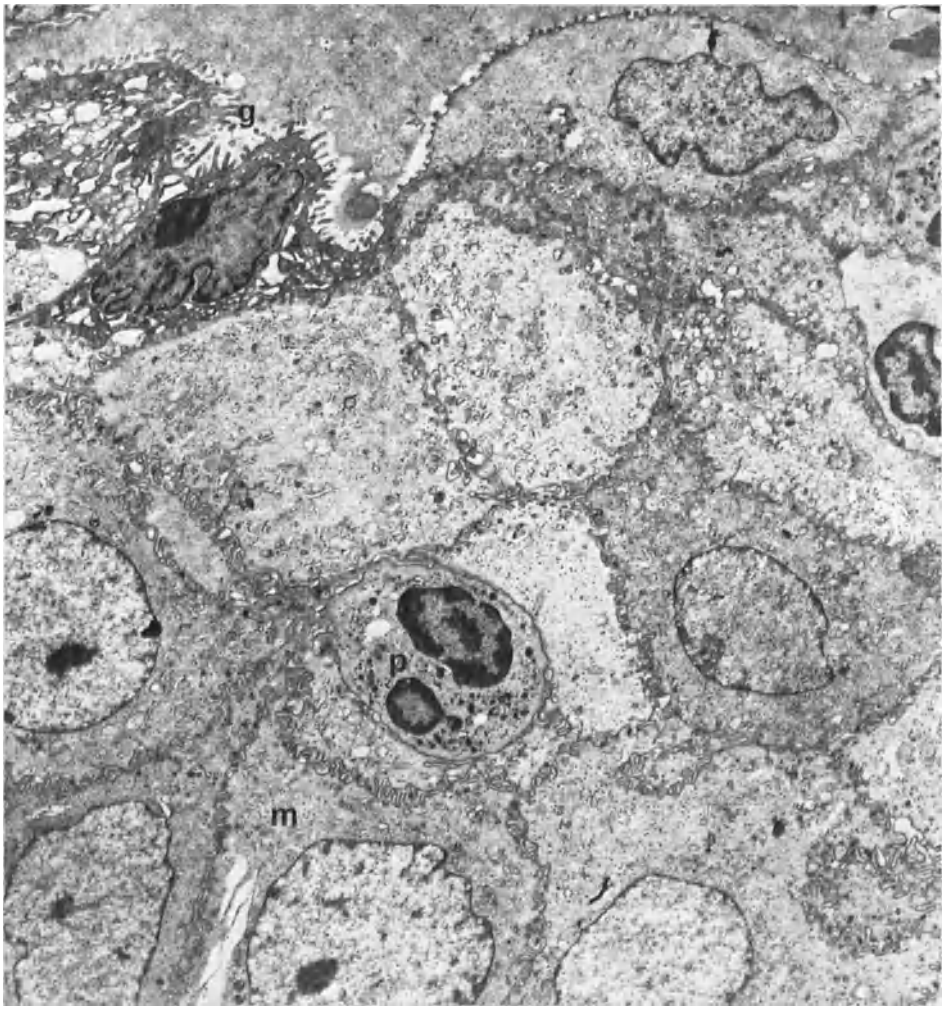


Fig. 15. Incomplete squamous metaplasia. *m*, metaplastic cells of polyhedral shape; *g*, glandular cells overlying the stratified epithelium; *p*,, polymorphonuclear leucocyte. × 5900

dysplasia. With that classification, the group of dysplasias therefore contained premalignant lesions, as well as harmless and reversible epithelial abnormalities. The concept of "dysplasia–carcinoma in situ" has had a major impact on the way gynecologists perceive precancerous lesions of the uterine cervix. In many instances the subdivision has been understood as being based on fundamental differences in etiology and behavior of the lesions. Dysplastic epithelia have often been considered harmless lesions reguiring little or no therapy, whereas lesions classified as carcinoma in situ demanded energetic, if not radical, treatment. The procedures used were based on the clinician's faith in the pathologist's ability to identify such lesions consistently and accurately (*Koss* 1978).

In recent years extensive studies of topography (*Burghardt* and *Holzer* 1970; *Burghardt* 1972), cell behavior in tissue culture (*Richart* et al. 1967; *Wilbanks* 1969), DNA and chromosomal analysis (*Sandritter* 1964; *Wilbanks* et al. 1967; *Richart* and *Wilbanks* 1966; *Wakonig-Vartaaja* and *Hughes* 1965; *Sachs* et al. 1972), ultrastructural investigation (*Shingleton* et al. 1968; *Stegner* 1978), and clinical follow-ups (*Koss* et al. 1963; *Richart* and *Barron* 1969; *Stern* and *Neely* 1963; *Jordan* et al. 1964; *Villa Santa* 1971) have revealed that, from a biologic standpoint, dysplasia and carcinoma in situ are closely related, regardless of their cytologic and histologic grading. In other words, the various degrees of precancerous dysplasia (mild, moderate, and severe) do not represent grades of malignancy but rather different histologic manifestations of identical malignant potential. Corresponding to invasive carcinomas of the cervix, precancerous epithelia have a spectrum of "dedifferentiation," which can be demonstrated far better by means of electron microscopy than by conventional histologic methods.

D. Ultrastructure of Precancerous Lesions

The most striking features have been described by a number of researchers (*Berger* et al. 1958; *Glatthaar* and *Vogel* 1958; *Ashworth* et al. 1961; *Luibel* et al. 1960; *Moricard* and *Cartier* 1964; *Younes* 1968; *Shingleton* et al. 1968; *Williams* et al. 1973; *Langley* and *Crompton* 1973; *Stegner* and *Pape* 1973; *Shingleton* and *Lawrence* 1976; *Wilbanks* and *Shingleton* 1976; *Stegner* 1978). In contrast to normal squamous epithelia, there are significant differences in the amount of cell-specific organelles (fibrils, glycogen granules), the distribution of nuclear chromatin, the outline of nuclear and cytoplasmic membranes, and the mode of cellular attachment. Both types of precancerous epithelia show distinct basement membranes running parallel to the basal cell layer. The cell nuclei are enlarged, and nuclear profiles are irregular, with deep invaginations of the nuclear membranes. The chromatin is coarsely distributed, and nucleoli are often abnormally large. Cytoplasmic glycogen is scarce or absent. Ribosomes are accumulated and often arranged in aggregates. Desmosomes are less numerous and sometimes poorly formed; tonofibrils are correspondingly fewer. The small number and imperfect differentiation of desmosomes result in increased cell desquamation. In both dysplasia and carcinoma in situ, the nuclear-cytoplasmic ratio is increased in the basal layer (Fig. 16).

Cells of *dysplastic epithelium* lack normal polarity. Their nuclei are highly pleomorphic and often multilobulated (Fig. 17). They vary considerably in size and shape; giant nuclei and multiple nuclei may be present. The cytoplasm may contain small amounts of glycogen. Tonofibrils are rare and irregularly distributed. The adjacent cell membranes are closely attached to each other and form interdigitations. The desmosomes are small, varying in number, and their attachment plaques are incompletely formed. In *carcinoma in situ* dedifferentiation becomes maximal. The cells, however, are more uniform than in dysplastic epithelia. The nuclei are oval and less pleomorphic, their long axis arranged vertically to the basement membrane (Fig. 18). The cytoplasm is rich in free ribosomes and mitochondria; other specific organelles (fibrils, glycogen granules) are rare or absent.

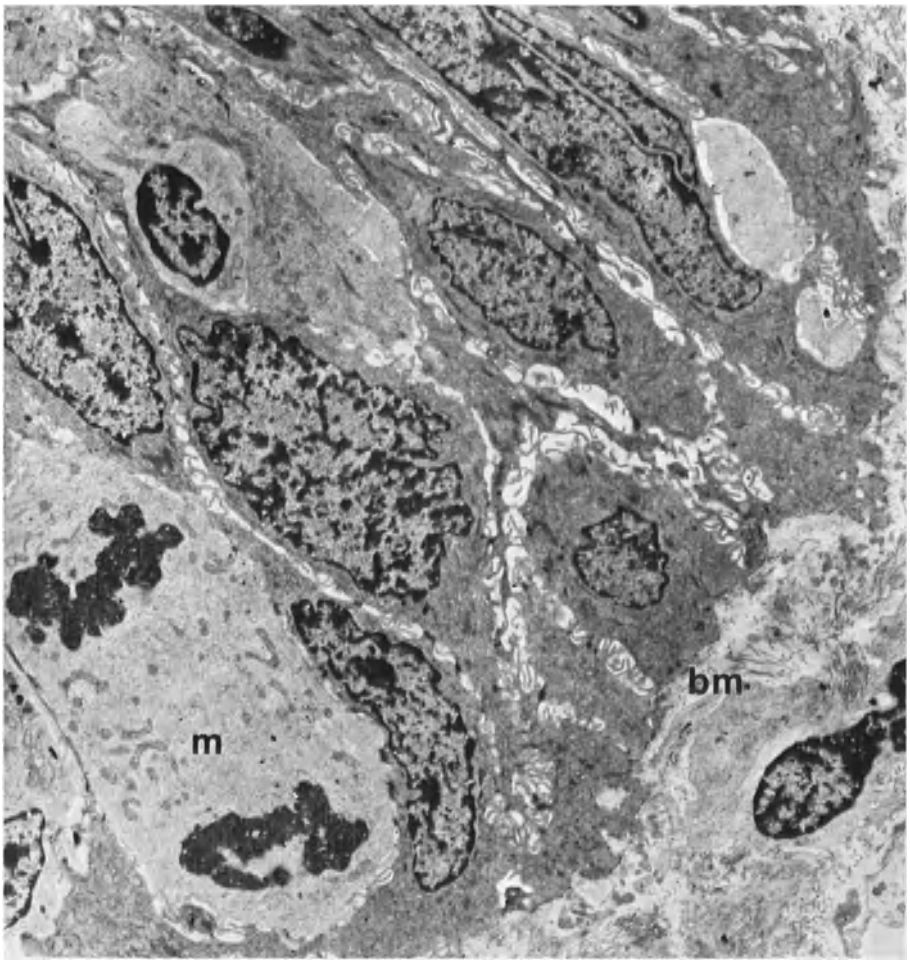


Fig. 16. Basal layer of an undifferentiated carcinoma in situ. Nuclear–cytoplasmic ratio is increased. Cell nuclei show coarse heterochromatic structure. *m*, mitotic cell; *bm*, intact basement membrane. × 6100

In addition to the essential deviations described above, a great variety of morphological patterns may occur in precancerous epithelia. As with invasive carcinoma, more or less differentiated types of carcinomata in situ can be distinguished, whereby corresponding to invasive cancer, the main differentiation products are mucin or keratin (*Stegner* 1978) (Fig. 19). On the ultrastructural level there is no clear demarcation between highly differentiated carcinoma in situ and various types of marked dysplasia.

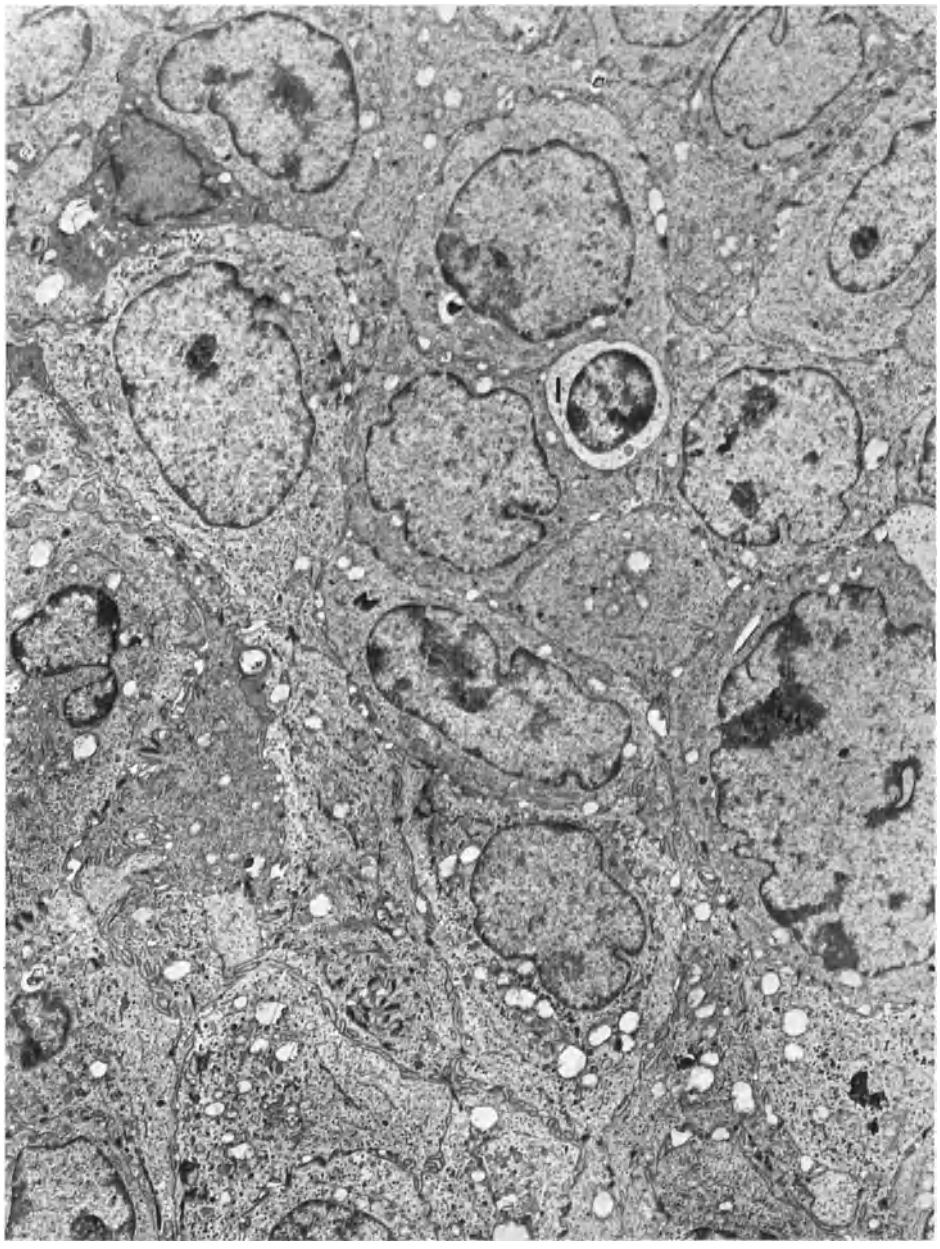
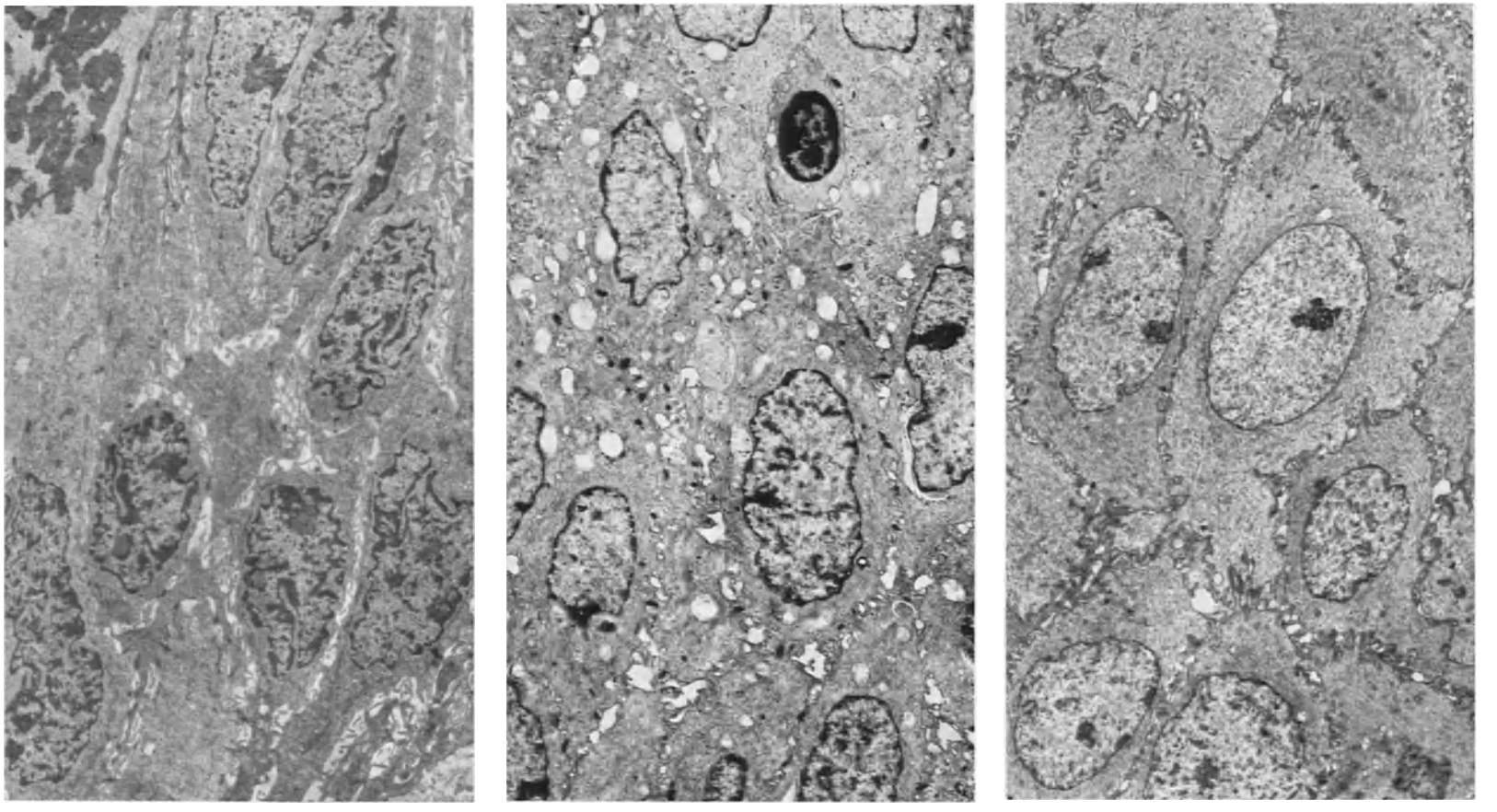


Fig. 17. Marked dysplasia. Cell nuclei are highly pleomorphic and lobulated. Cytoplasm contains small amounts of glycogen. Adjacent cell membranes are closely attached to each other and form interdigitations. Desmosomes are small. *l*, enclosed lymphocyte. × 7000



a b c

Fig. 18a—c. Various types of carcinomata in situ. **a** Anaplastic (small cell) type. **b** Intermediate type. **c** Epidermoid (large cell) type. × 5700

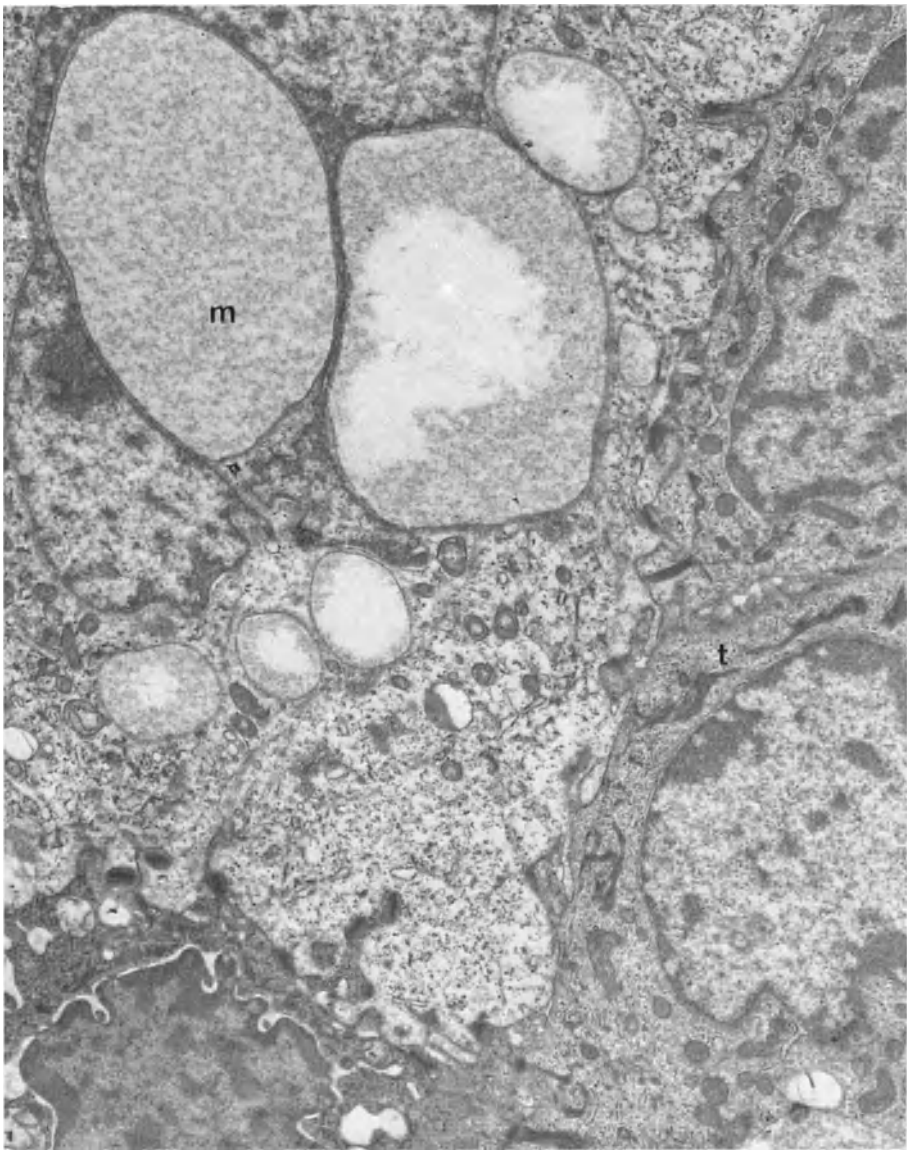


Fig. 19. Mucoepidermal type of carcinoma in situ. *m,* mucus vesicle; *t,* tonofibrils. x 13 500

E. Proposals for a New Classification

Acknowledging the spectrum of histologic appearances, several authors have proposed a further subclassification of precancerous epithelia on the basis of both histologic and cytologic criteria. *Bajardi* (1961) described undifferentiated and differentiated carcinoma in situ. *Reagan* and *Harmonic* (1956) distinguished a small and large cell type of carcinoma in situ from less anaplastic lesions, classed as atypical hyperplasia or dysplasia. A similar subclassification has been adopted by *Patten* (1969). *Fluhman* (1961) has suggested three types. Various degrees of differentiation and even keratinizing cell types are included in the classifications proposed by *Gore* and *Hertig* (1964), *Tweedale* and *Roddick* (1969) and *v. Haam* and *Old* (1964).

Although convenient for descriptive purposes, each subclassification lacks clinical significance unless it can indicate clear differences in the biologic potentials of the lesions. On the other hand, it should be kept in mind that further knowledge of the natural history of preinvasive and invasive cancer could only be gained from a subtle description and classification of epithelial abnormalities, thereby providing a growing understanding of the prognostic significance of various dubious lesions. Because of the impossibility of clearly differentiating them, it seems questionable whether an arbitrary distinction between dysplasia and carcinoma in situ should be further maintained. There seems little doubt that with respect to their biologic behavior dysplastic epithelia are, at least in part, true carcinomata in situ (*Burghardt* 1972). In approximately 80% of the cases both lesions are found in combination, the dysplastic epithelia in general being located distal to the carcinoma in situ, a regularity which has not yet been convincingly explained.

For the biologic reasons just summarized and because of the difficulties in establishing a clear and reproducible subclassification of prognostic value, *Richart* (1967) has proposed the term cervical intraepithelial neoplasia (CIN) for all lesions that are suspected to be potential precursors of cervical carcinoma. According to that concept, the degree of cytologic or histologic abnormality should be expressed by grades from I to III or IV as previously suggested by *Koss* (1978). The "single disease concept" would greatly diminish diagnostic differences and offer a more practicable basis for therapeutic approaches. A similar classification has been presented by *Stegner* (1978), but it favors retaining the term carcinoma in situ, which is now widely adopted. In a more comprehensive interpretation of carcinoma in situ, all precancerous lesions of the cervix uteri should be grouped under that term, which could then be subclassified into the following three categories:

1. Anaplastic type
   a) Small cell type
   b) Undifferentiated type
2. Intermediate type
   a) Large cell type
   b) Mucoepidermal type
3. Epidermoid type
   a) Keratinizing type
   b) Dysplasia of higher grades

Such a definition would include the anaplastic types as all grades of mucoid or epidermoid differentiation. According to this proposal, the term dysplasia would be used only for those lesions of minimal epithelial disorder including mild virogenic (koilocytotic) dysplasia which are apparently not involved in carcinogenesis or are supposed to regress spontaneously. Their surgical removal would be mandatory only if they persist as proved by adequate control study by means of cytology and colposcopy.

Acknowledgment. I wish to thank Mr. H. Strecker for skillful technical assistance.

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Therapy

Surgical Procedures

A.C. ALMENDRAL and O. KÄSER

A. Introduction

Operations are performed on patients with premalignant conditions, early invasion, or clinical cervical carcinomas: (1) for primary therapy, (2) to confirm the extent of the tumor (surgical staging), (3) to treat persistence, recurrences and metastases, (4) for therapy of sequelae or complications after treatment, and (5) to relieve symptoms caused by incurable carcinomas (e.g., hemorrhages, postrenal uremia, ileus, pain). No single surgeon can master all the relevant surgical techniques. For this reason, cooperation between different disciplines is an absolute requirement for an adequate solution to the problems arising.

This chapter is not intended to describe surgical technique or all available and usable procedures, but rather only the fundamentals and the indications for the most important operations. The reader is referred to the surgical literature for technical details (*Grewe* and *Kremer* 1977; *Hell* and *Allgöwer* 1976; *Kaeser* et al. 1973; *Mattingly* 1977; *Mayer* and *Zingg* 1973; *Nelson* 1977; *Novak* 1978; *Ober* and *Meinrenken* 1964; *Parsons* 1968; *Reiffenstuhl* 1974; *Spratt* et al. 1974; *Zenker* et al. 1975).

Hospitals and doctors who undertake treatment of a patient with the diseases mentioned above must be in a position:

1. To solve satisfactorily the *diagnostic problems* associated with these diseases. In the premalignant and early stages, efficient cytologic and histopathologic laboratories are required as well as experience in colposcopy. In clinical carcinomas, appropriate experience in gynecological oncology and a well-equipped X-ray diagnostic center with facilities for vascular diagnostics, ultrasonic techniques, and computer tomography are necessary.

2. To have available the methods for radiologic and surgical treatment as well as the required personnel, instruments and organization. The quality of the primary treatment makes a crucial contribution to avoiding high morbidity and to improving the rate of survival. Therapy of recurrent disease and complications is even more dependent on appropriate equipment.

3. To carry out continuous surveillance for early diagnosis of recurrences and to have experience with the social and psychological problems of cancer treatment.

4. To conduct *medical care of incurable cases.*

These prerequisites are found only in large centers. The question is discussed again and again as to whether the hospitals available in Central Europe are adequate for management or whether the task could be better met by cancer centers in which all the modern diagnostic and therapeutic equipment is available. Centralized or decentralized cancer treatment is a much-discussed problem. Both have their advantages and disadvantages; these will not be discussed here.

B. Operations for Primary Treatment

Optimum therapy of the premalignant conditions, of the early invasive cases and "clinical" cervical carcinoma is a topic which has been much discussed. The result of treatment probably depends less on the radicality and the modalities of therapy than on the extent of the disease and its biologic behavior. It will depend to a certain extent on the experience and skill of the therapist (*Castaño-Almendral* and *Kaeser* 1969).

The modern trend is to individualize therapy. This means that the specific treatment for each patient must be chosen by taking into account above all the histologic and biologic peculiarities of the lesion and its extent. The appraisal also encompasses the general situation (age, reproductive ambitions, general condition, etc.), the risks of the therapy to be applied as well as the available possibilities for carrying it out (*Friedberg* et al. 1972; *Ober* 1978).

A crucial concern of modern therapy in preinvasive and early invasive cases is the search for the "minimal effective and safe treatment," i.e., for the treatment method which guarantees a high chance of cure and at the same time avoids the risks of radical measures. At present, the danger of overtreatment in these cases is considerable and unnecessary mutilations and damage are frequent.

The individual therapy in clinical carcinomas (stage Ib to IV) is mainly determined by the invasion of the tumor and by the results of a thorough general examination. The extent of the carcinoma before the beginning of treatment is also the basis of clinical staging, which should be undertaken according to the guidelines of the cancer committee of the FIGO.

Beyond the stipulated diagnostic procedures, in our opinion other methods which are not admissible by FIGO for staging should be used for a more exact determination of the tumor extent. This enables a more adequate therapy (see Sect. C).

According to the last Annual Report (Fig. 1; for reference see *Kottmeier* 1979), treated cervical carcinomas show a rising recovery rate. These are partly attributable to improved treatment methods, but also to other unknown factors. It must be pointed out in this connection that invasive cervical carcinoma is becoming rare in Western civilised countries. In addition, the numbers of advanced cancers are decreasing in favor of earlier stages. This fact can be documented well for stages I and III on the basis of the figures in the Annual Report (Fig. 2). To date, there are no satisfactory explanations for these observations (*Ober* 1977).

I. Premalignant Lesions and Early Invasion

It is common to all these diseases that they cannot be detected with conventional diagnostic techniques such as inspection and palpation. The cytologic smear of the cervix is considered to be the most significant method for detection of these lesions. The number of false positive findings is 5%–10% and the false negative findings can be reduced to a minimum by suitable sampling technique and repeated investigations (*Kaeser* and *Szalmay* 1976).

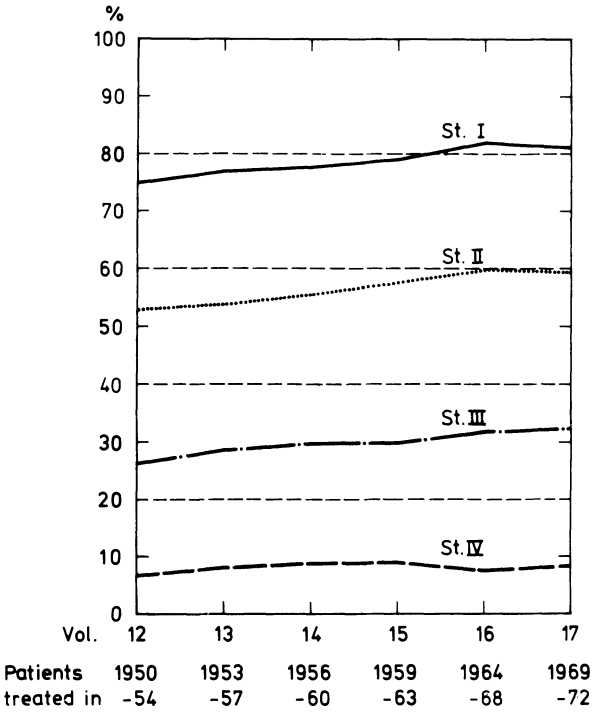

Fig. 1. Recovery rates of treated carcinoma of the cervix (Annual Report, 17th volume)

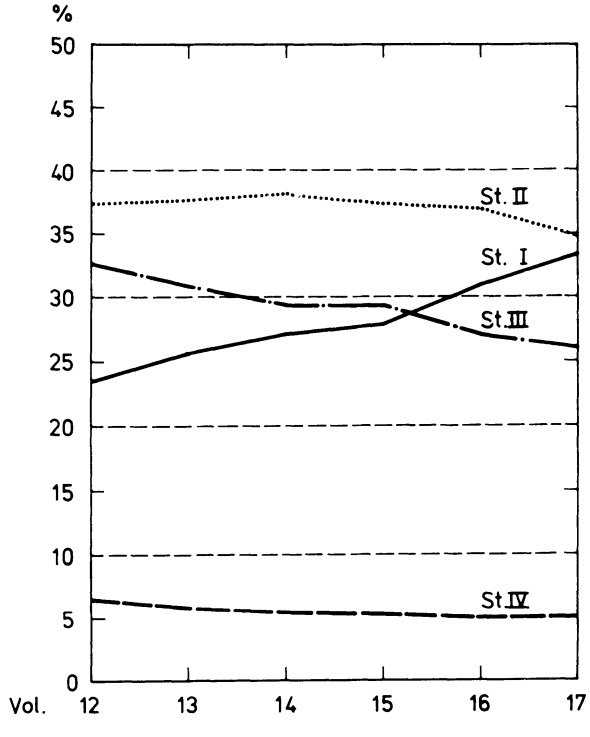

Fig. 2. Distribution by stage as percentages of total number treated (Annual Report, 17th volume)

In pathologic or repeated abnormal and suspect cytologic findings, further diagnosis is indicated. A close cooperation between cytologists and clinics is significant here. This is necessary because the cytologic nomenclature is non-uniform. In addition, the cytologists can give information as to the kind of intraepithelial atypia which is present, as to whether an invasion is to be expected, and as to where the lesion is located. This is of special significance when the morphology of the suspect cells indicate adenocarcinoma. In such a case, a fractionated curettage is indicated in order to distinguish between an adenocarcinoma of the cervix or the endometrium. If the results of the biopsy are negative, the possibility of a tubal or ovarian carcinoma should be considered (*Castaño-Almendral* 1969).

Measures for histologic diagnosis of abnormal and suspect cytologic findings are: four-point biopsies or multiple punch biopsies, possibly combined with endocervical curettage, multiple biopsies of iodine-light areas after the Schiller test and cervical curettage, portio scraping and cervical curettage, colposcopically pinpointed biopsies, in some cases combined with cervical curettage, and all more or less extensive excisions which are referred to under the collective term "conization." The choice of one of these methods depends among other factors on the position of colposcopy and cytology in the program of early diagnosis, on the peculiarities of each case, and on different opinions on the treatment of these diseases. The diagnostic and therapeutic results obtained depend more on individual experience than on the kind of tissue sampling. For this reason, the "pretherapeutic diagnostics" of these cases should be exclusively in the hands of those who are firstly, familiar with the problems and secondly, who carry out histologic investigations themselves or cooperate closely with a pathologist who has experience with this problem. Thirdly, the treating surgeon must be in a position to perform adequate individual therapy of the early cases.

Although it is generally accepted that the final histologic diagnosis is only possible on the basis of thorough investigation of the entire possibly diseased tissue, i.e., exclusively after conization, almost all other diagnostic procedures yield safe criteria which are sufficient for an adequate therapy. With the exception of blind quadrant biopsies with a rate of error of 14%–33%, the other biopsy methods have an accuracy of 95% and more, provided the material obtained is completely worked up histologically. A rate of errors of 0.3% has been reported for the colposcopically pinpointed biopsy. However, these figures are misleading. Thus 13% of all cases investigated colposcopically cannot be evaluated since the cylindrical-squamous epithelial conjunction cannot be completely visualized. Despite this limitation, this kind of pretherapeutic diagnostics leads to a decrease in purely diagnostic conization with its risks and makes possible a better individualized therapy. The application of colposcopy is an absolute condition for conservative treatment of epithelial atypias (*Burghardt* et al. 1978; *Coppleson* 1976; *Egger* et al. 1975; *Gitsch* et al. 1977; *Rummel* et al. 1976).

Colposcopically pinpointed biopsies together with endocervical curettage, which can be carried out without hospitalization and which are hardly a discomfort for the patient are the method of choice in our clinic for diagnosis of abnormal and suspicious cytologic findings. The combined evaluation of cytology, colposcopy and histologic findings in our 624 premalignant lesions and early cases checked histologically in the operation material, namely conus or uterus, lead to an inadequate treatment in less than 0.5% (three cases). The number of exclusively diagnostic conizations was reduced to less than 5% (*Castaño-Almendral* et al. 1974; *Heinzl* 1979; *Kaeser* and *Szalmay* 1976).

For the *treatment of bioptically verified premalignant and early invasive lesions,* various surgical procedures or local irradiation can be considered. In general, the surgical techniques are preferred because they far better permit graduated therapy and avoid the action of ionizing radiation on healthy tissue (e.g., bladder, rectum, ovaries). Adhesion of the vault of the vagina and interpretation of the cell picture after irradiation can give rise to difficulties.

1. Intraepithelial Atypias

These lesions range from slight, moderate, and high-grade dysplasias up to carcinoma in situ. They all represent a spectrum of the same disease, namely preinvasive cervical neoplasia. With some exceptions, the probability of further development up to invasion increases statistically with the degree of atypia. The histologic picture thus does not permit any definite inferences with regard to the prognosis of the individual case. In addition, the diagnosis of high-grade dysplasia or carcinoma in situ is frequently decided more by subjective than by objective criteria. For these reasons, *Richart* (1968) has suggested that all intraepithelial atypias should be classified under the collective term of *cervical intraepithelial neoplasia* (CIN). This nomenclature, which is used today by many authors, encompasses all three preinvasive lesions. The subdivision between grades I, II, and III expresses the degree of atypia and thus the probability of regression, persistence, or progression. In CIN III, the rate of progression in a period of observation of 1–7 years is likely to be between 30% and 55%. The rate of progression of CIN I and II is about 10%. This means that low-grade CIN also requires at least a cytologic and colposcopic control. Cases with signs of progression and those with CIN III should be treated.

The following approaches are available for treatment of high-grade intreapithelial atypias.

1. Physical destruction of the lesion (electrical diathermy, surgical diathermy, cryosurgery, CO_2 laser);
2. Local surgical extirpation (local excision, conization, or portio amputation);
3. Hysterectomy.

All these measures have the task of removal or destruction of the lesion. The following special features are significant for the choice of the method of treatment: nature, location and extent of the lesion; age of the patient; reproductive ambitions; wish for sterilization; other associated genital pathology, and the attitude of the doctor and patient. After each kind of treatment, cytologic and colposcopic controls must be carried out. These are the more important the more conservative the therapy has been.

a) Local Excision

Local excision can, in exceptional cases, be used to remove very small lesions which are visible colposcopically in their entirety. It is absolutely inadequate for therapy of the mostly extensive lesions and can hence be considered only in occasional, very selected cases (*Coppleson* 1976).

b) Vaginal and Abdominal Hysterectomy

This is the most frequently used operation in severe dysplasia and carcinoma in situ. It was formerly mostly performed secondarily after conization; at present, primary hysterectomy is applied more frequently. It may be performed only when cytology, colposcopically pinpointed biopsies, and cervical curettage have not given any indication of invasive carcinoma. In our view, hysterectomy (usually vaginal) is indicated:

1. When other genital problems such as menstrual disorders, prolapse, myoma, or adenomyosis uteri are present;
2. In carcinophobia or refusal of conservative treatment;
3. When there is a wish for sterilization;
4. In persistence or recurrence after conization or conservative treatment;
5. When uninterrupted follow-up is not guaranteed;
6. When there are doubts about the adequacy of histologic workup.

We make extirpation of a vaginal cuff dependent solely on the result of the Schiller test and colposcopy. Most authors advocate this or similar management (*Anderson* 1977; *Coppleson* 1976; *Singer* and *Jordan* 1978; etc.).

The increased danger of infection in hysterectomy performed between 48 h and about 4–6 weeks after conization should be pointed out in this connection. We advocate operating either within 28 h (rare) or after healing of the conization wound (4–6 weeks). Other authors attempt to eliminate the risk of infection in that they carry out any further surgical measures required on the basis of frozen sections subsequent to the conization in one sitting. However, rapid section investigation does not constitute an adequate histologic workup of cones.

c) Conization

Conization is the other alternative for treatment of severe dysplasias and carcinoma in situ and is probably the most frequently performed treatment. It is important to avoid conizations in false positive cytologic diagnosis and in cancers which are growing out beyond the microcarcinoma. The number of early and late complications after conization is not trivial. Late hemorrhages, inflammatory complications, and cervical stenoses are observed in 3%–22% of cases and are the more frequent the more extensive the conization. In a total of 386 conizations, we had complications in 41 cases (14%): these were hemorrhages in 11%, local infections in 5.8%, uterine perforations in 0.8%, and stenoses in 0.3%. In addition, the influence of conization on fertility and on future pregnancies and births cannot yet be precisely assessed. A conization which has been performed partly in healthy, partly in cancerous tissue possibly raises the danger of cancer propagation. These false indications can be kept within tolerable limits by careful clinical investigation and above all by use of colposcopy, pinpointed biopsy, and cervical curettage.

In conization, it is attempted to remove all of the altered tissue. It is therefore important to adapt conization to the special anatomic features of the individual case. One must take into account here:

1. That severe dysplasia and carcinoma in situ are very often extensive and reach far into the cervical canal, and

2. That the thickness and localization of the transformation zone, the site at which the pathologic process is located, show a different extent depending on the patient and alter in the course of life (*Burghardt* 1972; *Castaño-Almendral* et al. 1973).

Since the pathologic epithelium can be easily damaged, the portio is disinfected only by dabbing it with cotton wool soaked in disinfectant.

Before conization, no probing of the cervical canal or curettage should be performed. The basis of the conus is determined by the extent of the area which is iodine-light after the Schiller test or the colposcopically determined localization of the last cervical gland. The tip of the cone should be so high that about two-thirds (2 cm) of the cervical canal are extirpated along with it.

One proceeds by grasping the portio with two bullet forceps at 3 o'clock and 9 o'clock and drawing it forward. The cone is then cut out with a thin scalpel with slight sawing movements. Any injury of the easily damaged epithelium is to be carefully avoided. In order to reduce bleeding, it has proved useful to infiltrate the cervix with about 50 ml octapressin or adrenaline solution. After cutting out the cone, the entire wound surface is electrically cauterized. The cervical branches of the uterine artery are sutured and the conization wound closed with thorough sutures. We insert a Fehling tube into the cervical canal.

The histologic examination of the extirpated cone must answer the following questions: (1) What kind of epithelial atypias are present, what is their extent and localization? (2) Is there an infiltrative growth and if so what is its extent? (3) Have the epithelial atypias in the healthy tissue been extirpated? Satisfactory answers can only be expected when there is adequate histologic workup of the cone and it has been investigated in half serial sections (*Burghardt* 1972).

The *results of treating preinvasive cervical neoplasias with hysterectomy or conization* are excellent. Lasting removal of the lesion is achieved in more than 97% of the cases (*Anderson* 1977; *Castaño-Almendral* et al. 1974; *Coppleson* 1976; *Holzner* 1976; *Kolstad* and *Klem* 1976; *Kottmeier* 1979; *Kraus* et al. 1976; etc.). In the opinion of most authors the "recurrences" observed reflect spread outside the treated area which had not been diagnosed before the primary therapy (*Zippel* et al. 1974). Differences between hysterectomy and conization in this regard are slight.

These good results have led a few investigators to attempt to treat high-grade intraepithelial atypias with conservative methods. The lesions and the whole zone of transformation can be destroyed by physical techniques. The development of such methods was also necessary because young women (less than 35 years old) must be treated ever more frequently for dysplasias and carcinoma in situ.

Preconditions for conservative treatment of cervical intraepithelial neoplasia of a higher grade are definite pretherapeutic assessment of the altered epithelium and its extent as seen colposcopically. Furthermore, follow-up controls must be ensured. Such treatment comes in question above all in young patients who still desire to have children and has the advantage that it can be carried out without hospitalization.

The methods applied here are electrodiathermy, electrocoagulation, cryosurgery, and treatment with CO_2 laser.

d) Coagulation and Electrosurgical Cauterization

These methods lead to destruction of the epithelium by heat. The entire transformation zone and a portion of the cervical canal must be treated. The operation is performed under colposcopic control or in accordance with the result of the Schiller test. Although depth cannot be exactly controlled, coagulation should extend to the deeply situated glands, i.e., be a few mm in depth. It is appropriate to open nabothian cysts and coagulate their bases. Electrosurgical cauterization is a more radical intervention than coagulation. Healing of the wound requires 4–6 weeks. Complications such as hemorrhages, vaginal discharge, infections, and cervical stenoses are exceedingly rare and fertility is evidently hardly affected. The process of healing must be monitored colposcopically.

The treatment of intraepithelial neoplasias with electrocoagulation has a failure rate of 6.4%–9%. As with the other physical methods, this is largely determined by two factors: (1) the greater the extent of the lesion, the more frequent are failures and (2) failures occur above all in severe dysplasia and carcinoma in situ (*Coppleson* 1976).

e) Cryosurgery

Cryosurgery is a kind of physical therapy which makes use of very low temperatures. These cause a superficial destruction of the treated areas. The cone-like probes are cooled with carbon dioxide, liquid nitrogen, or Freon. The operating temperatures are –60°C–190°C. Use of liquid nitrogen is recommended for treatment of epithelial atypias, since the lowest operating temperatures and thus the necessary action in depth of about 3 to 4 mm is attained with this agent. The size and form of the probe is chosen according to the extent of the transformation zone and the morphology of the portio. The cooling time is 2–3 min. The white-colored zone of freezing should extend about 2 mm beyond the edge of the probe. The probe is removed after defrosting within a few seconds (*Townsend* 1976).

After the treatment, which does not cause any bleeding, the treated zone shows uniform alterations which can readily be seen. The destroyed epithelium regenerates within 4–6 weeks without noteworthy scar formation. The healing must be checked colposcopically. This intervention has a low risk and can be carried out without hospitalization or anesthesia. Its disadvantages are a more or less severe vaginal discharge lasting a few weeks, lack of full control of depth and shift of the squamous-cylindrical epithelial boundary in the direction of the endocervix subsequent to the operation (this makes colposcopic checkups more difficult).

We have been performing cryotherapy since 1975. We have so far treated 211 patients and followed them up for 3–40 months. Our success rate of 95% corresponds to recent literature data (Table 1). The poor results published earlier are partly based on an inadequate selection of patients and partly on technical deficiencies in performing cryotherapy. In our patient material, we have not yet observed any significant complications after cryotherapy. Occasional inflammatory complications have been seen. Reproduction, pregnancy, and delivery are not affected.

Table 1. Results of treatment of CIN with cryosurgery

Author	No.	Failure (%)
Crisp 1972	123	6.5
Tredway et al. 1972	118	19.0
Creasman and *Weed* 1980	75	30.0
Underwood et al. 1976	64	6.2
Lickrish and *Fortier* 1977	164	10.4
Einerth 1978	59	9.0
Kaufmann and *Irwin* 1978	395	11.1
Popkin et al. 1978	208	4.0
Szalmay and *Heinzl* 1979	211	5.0

f) CO_2 Laser

The most modern physical therapy of cervical epithelial atypias at present is application of CO_2 lasers. Laser is the abbreviation for "Light Amplification by Stimulated Emission of Radiation." Physically monochromatic infrared light is produced and focused at a point. The energy of the laser rays is absorbed by the tissue and causes an intracellular loss of water. Physical and biologic details may be found in the appropriate literature (*Anderson* 1977; *Baggish* 1980; *Bellina* 1979; *Stafl* et al. 1977).

The desired are can be destroyed with CO_2 laser under colposcopic control while the surrounding tissue remains unaffected. The required depth effect is attained by selection of different energies and by different duration of application. This therapy is completely painless. Advantages compared to cryosurgery are the accurately pinpointed destruction of the desired tissue portion, the shorter duration of healing, the lower wound secretion, and the lack of scar contraction. Disadvantages are higher costs of these instruments, immotility, and the necessary accompanying safety measures.

This method has also been applied recently in our hospital (Fig. 3). The success rate quoted in the literature averages 95% and corresponds to that of cryotherapy (Table 2).

Table 2. Results of treatment of CIN with CO_2 laser

Author	No.	Failure (%)
Stafl and *Wilkinson* 1977	50	10.0
Carter et al. 1978	45	8.9
Bellina 1979	247	4.4
Jordan 1979	121	5.0
Baggish 1980	115	4.3

To summarize, the physical methods can be regarded as a good alternative in the treatment of intraepithelial atypias. Correct choice of the patient and experience with colposcopy are decisive for good results. However, final evaluation is not possible at present since results with long-term observations are not yet available. The danger of

inducing invasive lesions or overlooking them can be designated as improbable. In any case, the physical methods are a good means of bridging an interval until definitive surgical removal (conization or hysterectomy).

2. Persistence and Recurrences of Epithelial Atypias

Persistence and recurrences after conization and hysterectomy are rare. The danger of a new manifestation of the disease is somewhat greater after conization than after hysterectomy. At all events, cytologic and possibly colposcopic control over a period of years are indicated since late recurrences are not rare. On the other hand, the danger of the genesis of an invasive carcinoma after these treatments is exceedingly rare. According to a literature compilation by *Coppleson* (1976), with a total of 12 675 cases, most of whom were observed for at least 5 years, 0.24% invasive carcinomas were diagnosed after local excision by conization or portio amputation and 0.39% after hysterectomy. The difference between local excision and hysterectomy is not statistically significant. The figures in the 17th Annual Report are similar (*Kottmeier* 1979).

Recurrences after conization are usually treated by hysterectomy, possibly including a vaginal cuff. A new conization can also be carried out in selected cases. In *recurrences after hysterectomy,* a conservative therapy should be aimed for. Treatment with CO_2 lasers is most suitable here. In extensive disease, a partial colpectomy cannot be avoided.

3. The Pathologic Cervical Smear in Pregnancy

The cytologic control of the pregnant woman is just as important as that of the nonpregnant woman. The measures required for histologic verification of the pathologic and suspect cytologic findings in pregnancy and eventually for treatment depend on many factors, namely the histologic cell type, duration of pregnancy, urgent desire for children, and the possibility of applying colposcopy (*Barber* and *Graber* 1974; *McGowan* 1978).

Colposcopy is being used increasingly in the assessment of a pathologic cell smear in pregnancy. It makes it possible to dispense with conization and cervical curettage in the majority of cases. Unequivocally pathologic colposcopic findings are clarified histologically by an excision biopsy. If an invasive carcinoma is detected here, the appropriate therapy should be instituted. In all other epithelial atypias, one can delay treatment until after the delivery. Continuous cytologic and colposcopic controls are necessary. With this mode of clarification, the frequent complications of a conization during pregnancy, namely hemorrhage, abortion and premature birth, can be avoided. Colposcopic examination and thus assessability of the entire zone of transformation is possible in almost all cases because of the hormonally induced ectopia in pregnancy.

II. Early Invasive Cases (Stage Ia and "Microcarcinoma")

The question which tumor size and which histologic characteristics such as depth invasion, growth type, infiltration of the lymphatic and blood vessels, inflammatory alterations, etc. make necessary the full radiological or surgical carcinoma treatment is answered variously. A reason for the controversial therapy of these cases is partly that a generally recognized histologic nomenclature is lacking. The treatment results for these diseases published in the literature are therefore hardly comparable.

The results of *Lohe* (1974, 1978) and those from various literature compilations (*Anderson* 1977; *Briggs* 1979; *Lohe* et al. 1978; *Rummel* et al. 1976), however, show uniformly that lymph node metastases are exceedingly rare in doubtful or early stroma invasion. The number of positive lymph nodes in invasive carcinomas which have not exceeded a depth of 0.5 mm, a length of 10 mm, and a breadth of 0.5 mm (tumor volume 500 mm^2) is distinctly below 1%. The risk of dying of an early stroma invasion is very low and probably less than 0.5%. On the other hand, the cancer mortality in microcarcinoma is somewhat higher, about 3%. The cure rate of all these cases is 95% and above. The differences between the results attained with conservative or radical treatment methods are not statistically significant.

Decisive for adequate treatment of early invasive carcinomas is a careful histological workup of the cones and close cooperation with an experienced pathologist. If this is not possible, complete surgical or radiation therapy should be performed in the case of every invasive lesion.

These facts show that complete local extirpation of the lesion is sufficient for treatment of *epithelial atypia with early stroma invasion.* Therapy consists of conization in young women desiring to have children or in other cases of vaginal or abdominal hysterectomy possibly including a vaginal cuff when the disease extends into the vaginal wall.

A more differentiated therapeutic procedure corresponding to the special morphological features appears to be advisable in *small invasive carcinomas.* In the majority of these cases, a reduced therapy is probably sufficient: a simple hysterectomy, a somewhat extended abdominal or vaginal hysterectomy with a parametrial and vaginal cuff. The value of an additional pelvic lymphadenectomy is not known. The lymph nodes are rarely affected and the influence of lymphadenectomy on the rate of cure can be insignificant. On the other hand, extirpation of the most frequently affected lymph nodes, namely the iliac, external and obturator areas does not constitute an additional surgical risk. In preoperatively demonstrated tumor invasion into the vessels, full carcinoma therapy is necessary in the opinion of most authors. In exceptional cases, if clear proof is available that the carcinoma was extirpated by the conization, further treatment can be dispensed with in young women wishing to have children (*Lohe* 1974; *Lohe* et al. 1978).

III. Surgical Treatment of Clinical Cervical Carcinomas (Stages Ib–IV)

After a carcinoma has exceeded microscopic dimensions, only full cancer therapy can be considered. There are three possibilities: (1) exclusive (mostly combined) local and percutaneous radiotherapy; (2) surgical procedures; and (3) various combinations of irradiation and surgical measures. The rates of recovery with these different kinds of treatment hardly differ from each other. Furthermore, no decision can be made whether the different kinds of therapy cure the same carcinomas and fail in the others, or whether the results might be improved by more selective therapy. Experience shows that some collum carcinomas persisting or recurring after radiotherapy can be cured by surgery and recurrences after surgery can be cured by retrospective irradiation. The number of these cases is small and therefore does not appreciably influence the overall 5-year results. One-third to one-half of patients with a clinical carcinoma cannot be cured (*Castaño-Almendral* and *Kaeser* 1969).

1. Evaluation of Treatment Methods

Analysis of the efficiency of individual treatment methods is difficult due to numerous factors such as the dissimilarity of patient material, establishment of the indication, details of treatment methods, etc. For these reasons and for lack of prospective randomized studies, it cannot be decided which treatment – operation, irradiation, or combined therapy – achieves the highest rate of cure. If the statistical data do not permit an unequivocal answer to the question of the best therapy, it is nevertheless incon-

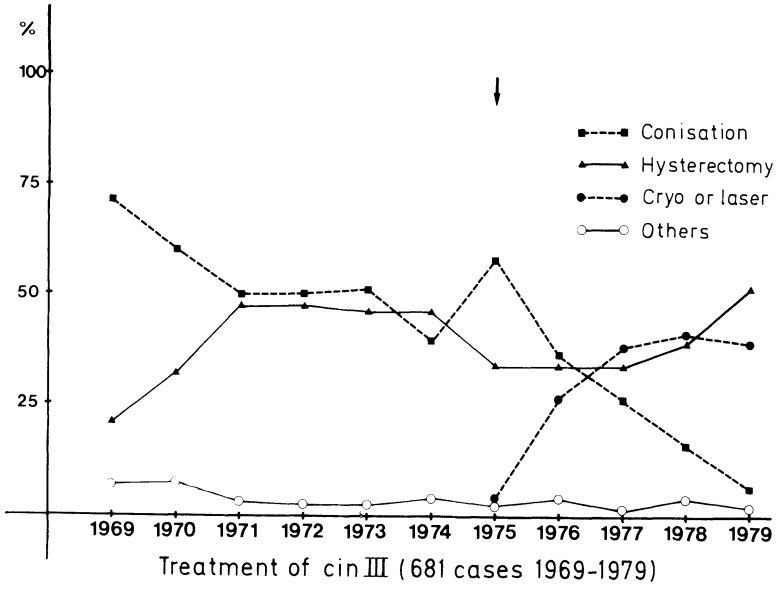

Fig. 3. Changing concepts in treatment of severe dysplasia and carcinoma in situ by using cryosurgery and CO_2 laser (Women's University Clinic, Basel)

tested that radiotherapy is the only primary treatment possible for many or most cervical carcinomas. This is either because the carcinoma is already advanced or because the general condition of the patient does not permit a large operation.

Statistical comparison of the 5-year cure rates of different institutes entails numerous possibilities of error, but is necessary in order to obtain an overall view. According to the results published in the Annual Report, there is no correlation between surgery rate and recovery rate in the locally operable cases. Some hospitals with a high operation rate report the highest recovery figures, but other hospitals with low operation frequencies attain almost the same results (Fig. 3). However, there are no great differences between the vaginal and abdominal procedure of surgical therapy, either in patients with or without additional lymphadenectomy. A distinct improvement in the cure rate could be achieved neither with systematic preoperative irradiation nor with systematic postradiologic lymphadenectomy in advanced cases. Because of its high morbidity combined with a very doubtful increase in efficiency, the latter method is rejected today (*Hamberger* et al. 1978; *Rutledge* et al. 1976; *Stallworthy* and *Wiernik* 1976; *Weed* and *Holland* 1977).

2. Advantages and Disadvantages of Surgical Treatment

In favorable general and local cases of stage Ib and IIa, there are some arguments which support surgery: (1) The possibility of graduating carcinoma treatment. Whereas the full curative dose is always given in radiotherapy and a not insubstantial morbidity must be accepted, the radicality of the operation can be adapted to the individual case. When the parametria, lymphatics and lymph nodes are free of carcinoma, postoperative irradiation with its risks for the bladder, intestine and ureters can be omitted. (2) Histologic examination of the surgical preparation, especially the condition of the pelvic lymph nodes, permits a very reliable prognosis. (3). The operation permits the function of the ovaries to be preserved. There is no raised risk of recurrence when the ovaries are retained. (4) Preservation of a functionally efficient vagina is achieved above all by early postoperative treatment (retraction, stretching, estrogen-containing ointment, and tamponade). (5) The side effects of radiotherapy, the danger of "radioresistance" and radiation-induced carcinogenesis can be avoided by operation. (6) The duration of the treatment and the costs of surgery are lower (*Barber* 1978; *Rutledge* et al. 1976).

A disadvantage of surgical therapy compared with radiotherapy is the higher rate of primary complications. This probably applies to a larger extent to abdominal than it does to vaginal surgery. However, the abdominal procedure will be preferred if one believes in the significance of lymphadenectomy for improvement of the remission rate. The postoperative mortality of comparable cases is higher than after irradiation, although it could be markedly lowered in recent years in some hospitals, where it is today 1% or less. We ourselves had a mortality of under 0.5% in more than 1000 operations for cervical carcinoma. A further crucial advantage of radiotherapy is the low number of urinary tract fistulae, which, however, could be markedly lowered in Wertheim operations. Otherwise, the morbidity of surgical and radiotherapy is different and cannot be readily compared. This applies above all for late complications, of

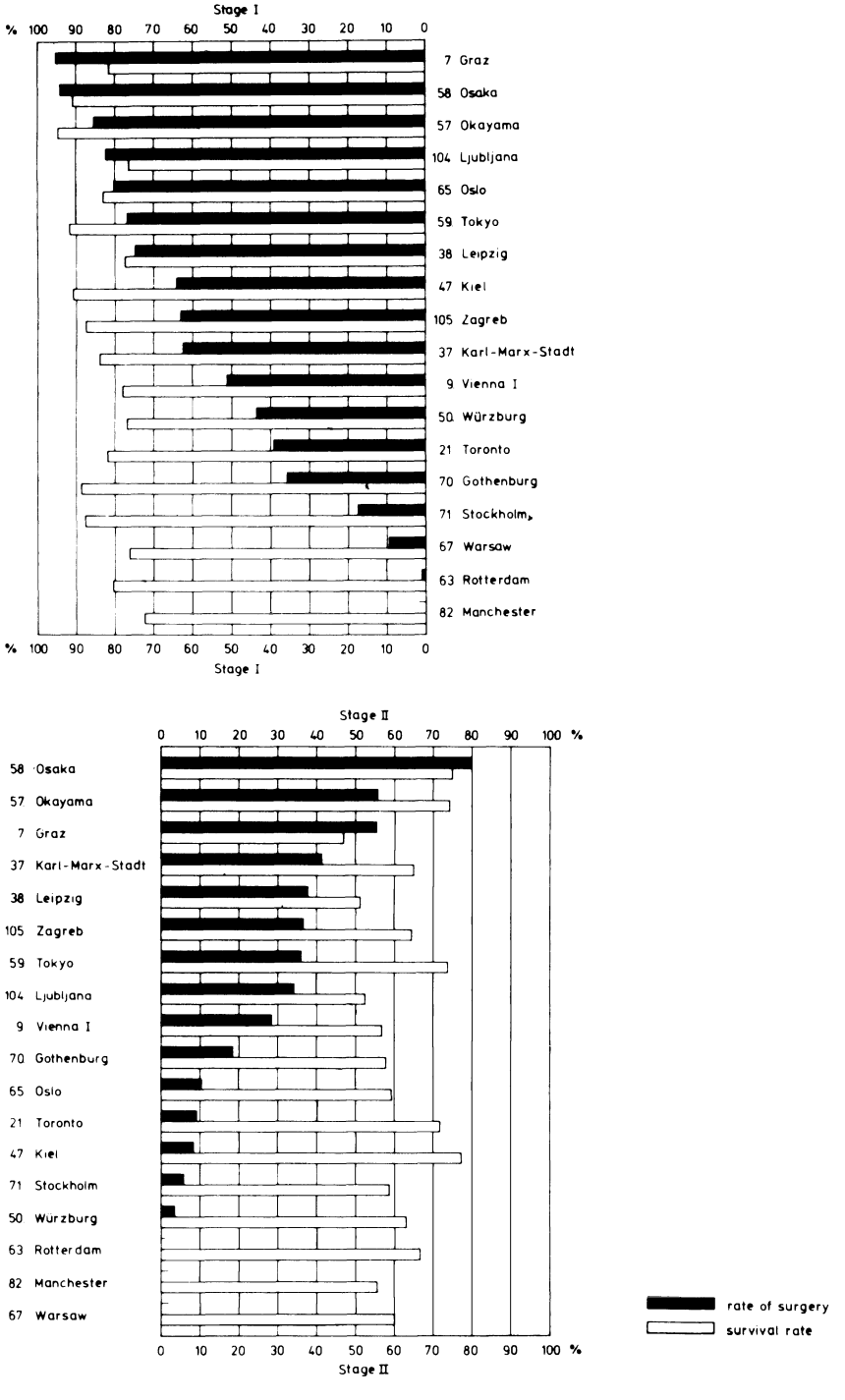

Fig. 4. Rate of surgery and survival rate of patients with carcinoma of the cervix (Annual Report, 17th volume)

which there is quite a large number with both methods. Late deaths which are entirely or partially due to the therapy are observed with both methods (*Barber* 1978; *Beck* 1979; *Disaia* et al. 1975; *Friedberg* et al. 1972; *Kaeser* et al. 1973; *Peel* 1978).

3. Indications and Methods for Surgical Treatment

In our opinion, surgical treatment can only be considered when the disease is localized to the cervix or the immediate vagina (stage Ib and IIa), and the risk involved in surgery is not large. Appreciable obesity and an age of 70 years and more constitute contraindications. In unfavorable conditions for radiotherapy, such as uterine myomata, ovarian tumors, and prior pelvic infections, surgery should be given preference. An analysis of frequency of surgery in different hospitals shows large variations (Fig. 4). Besides objective criteria, subjective factors such as whether the surgeon has mastery of a particular method evidently affect the choice of therapy. However, it is desirable that the best treatment be chosen for the individual case.

The principles of surgical treatment of cancer are radical extirpation of the tumor and its immediate ramifications as well as removal of the primary lymphatic drainage areas. In the case of cervical carcinoma, this means extirpation of the uterus, of the parametria and part of the vagina, as well as of the pelvic lymph nodes. Only abdominally extended hysterectomy (Wertheim operation) meets these prerequisites. In vaginally extended hysterectomy (Schauta-Amreich operation), the important postulate of modern cancer therapy, namely to remove all lymph regions which are potentially affected cannot be fulfilled without additional operation (extraperitoneal lymphadenectomy). The majority of authors operate on cervical carcinoma exclusively or chiefly abdominally. The reader is referred to the literature for detail of the technique: *Kaeser* et al. 1973; *Mattingly* 1977; *Nelson* 1977; *Novak* 1978; *Ober* and *Meinrenken* 1964. Ureter preparation with preservation of the so-called mesoureter, Redon drainage, infection, and thrombosis prophylaxis as well as advances in anesthesia and recovery have appreciably reduced the risks of large abdominal cancer operations.

4. Treatment of Special Cases

a) Special Histologic Features

In principle, adenocarcinomas or other carcinomas with adenoid growth (Gartner duct carcinoma) are to be treated like squamous epithelial carcinomas. These tumors evidently have a poorer prognosis than squamous epithelial carcinomas (Table 3). An often suspected radioresistance probably does not exist. If the corpus uteri is involved, the decision as to whether it is a corpus carcinoma which has spread to the cervix or a collum carcinoma which has spread to the corpus can create difficulties. Application of histochemical methods can be useful here. Solution of this problem is important for radiotherapy (*Friedberg* et al. 1972).

Table 3. Results of therapy by histologic type and treatment applied (*Kottmeier* 1979)

Stage	Histology	Radiation alone			Surgery, alone or combined with radiotherapy		
		No. treated	5-year survival No.	%	No. treated	5-year survival No.	%
I	Epidermoid ca.	3230	2419	74.9	4204	3589	85.4
	Adenocarcinoma	188	114	60.6	352	279	79.3
II	Epidermoid ca.	6288	3567	56.7	2405	1660	69.0
	Adenocarcinoma	295	115	39.0	218	126	57.8
III	Epidermoid ca.	5715	1783	31.2	423	165	39.0
	Adenocarcinoma	257	44	17.1	36	10	27.8
IV	Epidermoid ca.	893	80	9.0	123	17	13.8
	Adenocarcinoma	67	5	7.5	18	0	0.0
Total I–IV	Epidermoid ca.	16 126	7849	48.7	7155	5431	75.9
	Adenocarcinoma	807	278	34.4	624	415	66.5

b) Pregnancy and Cervical Carcinoma

The incidence is 0.005%–0.2%. Difficult problems can arise in therapy, because not only medical criteria, but also psychological and religious factors play a role. Treatment must accordingly be adapted to the individual patient.

There are no signs that physiologic alterations in pregnancy favor the growth or metastasis of collum carcinoma. The prognosis is thus the same for the individual stages as for nonpregnant women. It is possibly made worse by the birth trauma and by hormonal changes. The criteria for establishing the indication for treatment are the same as those for nonpregnant women. If the baby is not viable, treatment should be commenced without delay. Under certain circumstances, maturation of the child can be waited for before commencing therapy. The procedure must thus be decided from case to case. It is important that good preconditions for radiotherapy are created even in inoperable cases by appropriate surgical measures (abdominal hysterotomy to empty the uterus and possibly a high amputation of the corpus). With a viable baby, a cesarian section is first performed and the carcinoma subsequently operated on or irradiated depending on its extent. A vaginal birth is at all events contraindicated because of the danger of hemorrhages, ruptures, infection, and propagation of the carcinoma. The results of treatment of collum carcinoma in pregnancy roughly correspond to those in nonpregnant patients (*Barber* and *Graber* 1974; *McGowan* 1978).

c) Invasive Carcinoma Discovered Retrospectively in the Histologic Specimen

Such cases occasionally occur because no surgical study was performed or the extent of the carcinoma was underestimated. The further procedure depends above all on the size of the carcinoma. A complementary surgical or radiologic treatment is indicated when the carcinoma exceeds microscopic dimensions. Removal of the parametria and a bilateral pelvic lymphadenectomy evidently give rise to better results than postoperative irradiation (*Kaeser* et al. 1973).

d) Cervical Stump Carcinoma

In principle, this carcinoma does not give rise to any particular problems. However, operation or performance of radiotherapy is made difficult by the unfavorable anatomic conditions. In favorable local cases, operation is often more advantageous, since the dose of radium must be kept low because of the nearness of the bladder and of the danger of damaging the bladder and intestine. Its prognosis depends less on surmounting these difficulties than on the degree of spreading of the tumor. Systematic performance of total hysterectomy can completely eliminate cervical stump carcinoma. If the intrafascial method is applied, total extirpation of the uterus generally does not involve major technical difficulties even with extensive fusions or Douglas endometriosis. Damage to the intestine, ureter, or bladder can be largely avoided with this technique (*Castaño-Almendral* and *Kaeser* 1969).

e) Total Prolapse and Cervical Carcinoma

Simultaneous occurrence of these diseases is extremely rare. Surgical treatment with simultaneous colpoperineoplasty is to be preferred to radiotherapy. In inoperable cases, the anatomic conditions appropriate for radiotherapy must be created by reposition of the uterus (*Kaeser* et al. 1973).

C. Establishment of the Extent of the Tumor

The cure rate of extensive cervical carcinomas treated with radiation (stage IIb to stage IV) has not appreciably improved despite introduction of megavolt therapy and refinement of the technique. According to various analyses, this failure is based above all on the inability to eliminate lymph node metastases. On the other hand, local relapses are exceedingly rare. A few failures of radiotherapy may be attributable to the presence of para-aortic lymph node metastases which were not diagnosed before therapy, since they are located outside the usual irradiation areas of percutaneous radiotherapy and are thus not subjected to the action of percutaneous radiotherapy (*Nelson* et al. 1974; *Rutledge* et al. 1976).

I. Methods of Detecting and Localizing Lymph Node Metastases

The most important methods of detecting and localizing lymph node metastases, of classifying them prognostically, and of selecting therapy are: *lymphography, cavography, ultrasound diagnostics, and computer tomography.* The most reliable and most specific technique is lymphography (*Castaño-Almendral* et al. 1974; *Gaudenz* and *Almendral* 1975; *Plentle* and *Friedman* 1971; *Zwicker* and *Alder* 1979). However, irrespective of the technique only suspicious or "positive" results are reliable. Negative results do not permit lymph node metastases to be excluded with certainty. These "false negative" results (30%–50%) of all histologically checked cases result from the following situations: (1) the tumor is small (less than 3 mm in diameter) and is not detected by the method; (2) lymph nodes massively infiltrated by tumor tissue are occasionally not shown up lymphographically; (3) the location of the affected lymph node is unfavorable; (4) a lymph node metastasis does not always lead to an enlargement of the lymph nodes and is therefore not detected by ultrasound diagnostics. On the other hand, a lymph node enlargement is not always due to tumor tissue. Indefinite lymph node alterations can sometimes be biopsied by needle under visual control by means of fluoroscopy or ultrasound examination and clarified morphologically (*Bonfiglio* et al. 1979; *Haaga* 1979).

In combined application of the methods mentioned above, a metastasis can be regarded as verified when pathologic alterations can be demonstrated with various methods at the same location. In such cases, as well as when there are unequivocal positive lymphographic findings, conclusions can be drawn with regard to therapy. For example, there is then an indication for irradiation of the para-aortic region. Routine irradiation of the lumbar region in extensive cervical carcinomas (stage IIb and more) cannot be recommended. This kind of irradiation has the disadvantage that the small intestine, part of the solar plexus, kidneys, and spinal cord are in the ray path. For this reason, and because of the large dose volume, such radiotherapy is associated with frequent and severe complications. An improved cure rate on the basis of this type of irradiation has also not been proved so far.

II. Surgical Staging

Because of the insufficient accuracy of the methods mentioned above in demonstrating lymph node metastasis, a few hospitals (chiefly in North America) have gone over to determining the extent of the tumor by means of laparotomy and biopsies (*Berman* et al. 1977; *Buchsbaum* 1972; *Piver* and *Barlow* 1977; *Rutledge* et al. 1976; *Wharton* et al. 1977). This procedure was first suggested by *Nelson* et al. (1974). The objective was a more adequate radiotherapy (altered irradiation fields) in cases of histologically demonstrated para-aortic metastasis. Some authors consider extensive cervical carcinomas in patients with a good general condition an indication for *"staging laparotomy."* A few hospitals also carry out this investigation in locally operable carcinomas. It is agreed that only the palpably enlarged or the readily accessible, non-suspect lymph nodes should be extirpated. Extensive lymphadenectomies combined with radiotherapy

have a prohibitive morbidity (50%) and mortality (15%) (*Wharton* et al. 1977). The results of this surgical staging (Table 4) show that para-aortic node metastases are found in about half of all cases of extensive carcinoma (stage III). The reported frequency of lymph node metastases in the para-aortic region is to be regarded as only a guide, however, since not all patients were examined surgically and a complete lymphadenectomy was not carried out.

Table 4. Incidence of aortic metastases after surgical staging

		Staging (%)			
	No. patients	Ib	II	III	IV
Averette et al. 1975	207	5	12	25	66
Buchsbaum 1972	34	–	5	18	33
Nelson et al. 1974	59	–	16	46	–
Piver and *Barlow* 1977	56	–	5	38	40
Ucmakli and *Bonney* 1974	49	–	5	18	33
Wharton et al. 1977	120	–	21	33	

Examination of the accuracy of clinical staging compared with the finding at laparotomy was undertaken in 207 of a total of 291 patients with cervical carcinomas (*Averette* et al. 1975). The surgical investigation consisted of laparotomy. Besides inspection and palpation of the abdominal organs and biopsy of suspicious findings, a bilateral para-aortic lymphadenectomy and extirpation of the suspicious lymph nodes in the pelvic region as well as biopsies of the perirectal and perivesical tissue were performed. The largest variations between clinical and surgical staging resulted in the stages II and III. These figures indicate the significance of surgical staging in locally inoperable cervical carcinomas. It cannot yet be assessed to what extent such a routinely performed laparotomy leads to a more adequate treatment and contributes to improvement of the rate of cure.

Up to now, the hoped-for improvement of the treatment results by irradiation of the para-aortic region in histologically demonstrated metastasis has not been confirmed. A few observations indicate rather that para-aortic lymph node metastases frequently constitute a manifestation of generalized disease.

Scalene biopsy appears especially suitable to demonstrate generalized disease. *Ketcham* et al. (1976) found occult metastases in 13% of advanced but still operable cervical carcinomas. They therefore demanded that all patients with clinical cervical carcinomas should be subjected to scalene biopsy before therapy. However, further investigations did not confirm such a large frequency of scalene metastases. From the results in the literature (*Buchsbaum* and *Lifshitz* 1976; *Delgado* et al. 1975; *Perez-Mesa* and *Spratt* 1976) and above all from the investigations of *Egger* and *Kupka* (1978) indications for scalene biopsy are: (1) palpable supraclavicular lymph nodes; (2) inoperable primary cervical carcinoma; (3) lymphographically demonstrated para-aortic metastasis; (4) relapses after operation and/or radiotherapy. Scalene biopsy is prognostically very valuable. No patient with scalene metastases lives longer than 2 years,

irrespective of the treatment carried out. However, scalene metastases do not constitute a contraindication for local palliative measures. In recurrences, an exenteration or a high-dose radiotherapy are only justified when scalene metastases have been excluded by biopsy.

Surgical staging can be assessed as follows: in the indications specified above, scalene biopsy should be performed first. Only in a negative finding is "staging" laparotomy reasonable. The indication for laparotomy should be carefully examined because of the relatively slight benefit resulting from it.

D. Surgical Treatment of Persistence, Recurrences, and Metastases

The reappearance of a treated cervical carcinoma at the site of its primary location or in the immediate vicinity is designated as recurrence when a symptom-free period of at least 6 months has elapsed between conclusion of the treatment and renewed manifestation of the tumor. Otherwise, one refers to further growth or tumor persistence. This distinction is purely conventional, since considered biologically a relapse is a special form of tumor persistence. Distant tumor colonies are regarded as metastases. These rarely occur in isolation, and are frequently the manifestation of disseminated diseases which may not be clinically detectable (*Castaño-Almendral* 1969).

One-third to one-half of the cervical carcinomas treated are not cured. The greatest number of relapses and metastases are observed within 3 years, and rarely 5 years and more after treatment. Provided that treatment is adequate, the probability of their occurrence is mainly related to the extent of the tumor at the first treatment and secondly depends on the biology of the tumor and the resistance of the host.

The following factors are of crucial importance for the choice of treatment in this tumor remanifestation:

1. *Histologic verfication* of clinical and radiologic diagnoses must be aimed for in all cases. Suspect findings which due to their location are accessible to the investigating eye (possibly with application of endoscopic techniques) can be relatively easily clarified histologically. More difficult diagnostic problems arise in the parametrium or in relapses or metastases localized at the wall of the pelvis. Histologic verification requires puncture and aspiration of material for cytologic or histologic investigations. In some cases, even diagnostic surgical interventions (e.g., laparotomy, thoracotomy) with biopsies of the suspect findings cannot be avoided. Morphological clarification is important because any treatment (whether surgical, radiologic, or chemotherapeutic) can cause severe side effects. These therapies are therefore only justifiable in histologically verified diagnoses.

2. *Tumor extent* is likewise of great importance for the decision on further therapy. The main question here is whether the disease is still localized, i.e., accessible to surgery or radiotherapy, or whether it is already generalized. Localized recurrences and metastases are curable at least in theory. On the other hand, in generalized disease a palliative effect is the most that can be attained.

Clarification of the extent of the tumor requires application of various, in some cases highly differentiated, methods of investigation: radiologic investigation of the

thorax and skeleton, excretion urogram, angiographic procedures (lymphography, arteriography, phlebography), nuclear medical and scintigraphic studies (bones, liver, skeleton, brain), ultrasound investigation of the liver, retroperitoneal space, and abdomen as well as computer tomography. Surgical investigations are also occasionally indicated (see Sect. C).

3. The *location* of relapses and metastases and their involvement of vitally important structures determine their surgical extirpability. For example, central pelvic relapses can be removed surgically only with great risk if there is tumor growth into the large vessels, muscle, fascia, and bone.

4. Furthermore, the *kind of prior treatment* must be considered. In cases of localized recurrences that have been fully irradiated, surgery is the only remaining possibility of cure (Fig. 5). In central and parametrial recurrences after operation, radiotherapy is to be preferred.

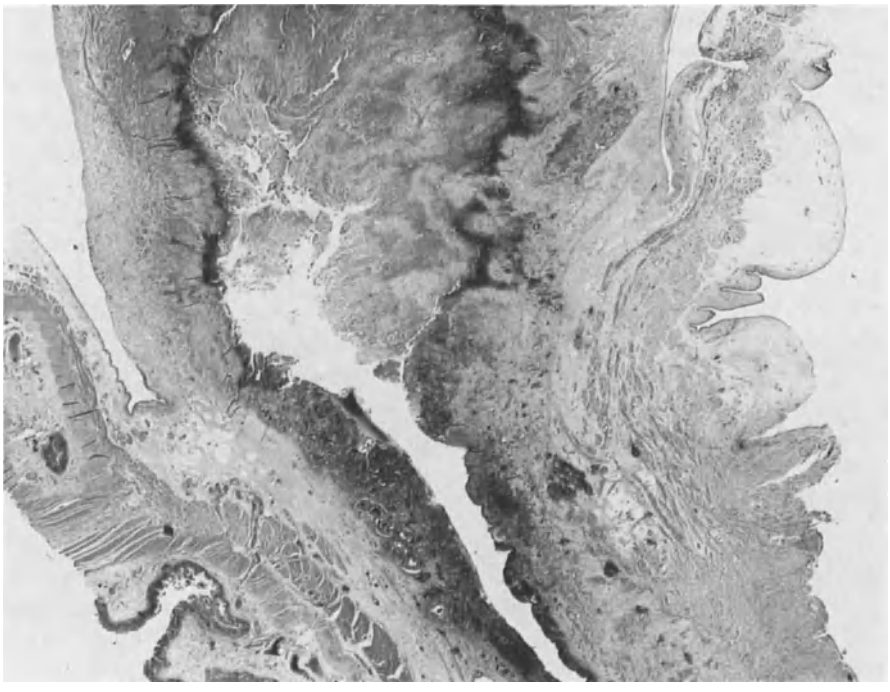

Fig. 5. Specimen of total pelvic exenteration performed for treatment of central recurrence after completed radiotherapy. The extension of the tumor to the bladder and rectum shows that an extended hysterectomy would have been insufficient to eradicate the lesion

5. Finally, in the choice of treatment the following factors must be considered: *age* of the patient, *poor general condition, concomitant diseases, unfavorable mental state,* etc.

It can be stated in summary that treatment of recurrences and metastases can only be decided on after careful assessment of the patient and her disease. The main prob-

lem here is whether there are still possibilities of cure in remanifestation of the tumor. Most recurrences and metastases are unfortunately only suitable for palliative therapy.

Surgical interventions in recurrences and metastases must be adapted to the individual case. The most frequently applied operations are hysterectomies of varying radicality and exenteration of the pelvis. Indications for surgical removal of isolated metastases are rare.

The most suitable operation for central pelvic relapses after operation and/or radiotherapy is *pelvic exenteration.* This comes in question mainly in local recurrences after radiotherapy and is to be preferred to extended hysterectomy because: (1) the combination of full radiotherapy with extended hysterectomy is associated with a high fistula morbidity; (2) in these recurrences, perivesical and perirectal tissue is frequently invaded by the tumor.

Pelvic exenteration can also be employed for primary treatment of extensive cervical carcinoma in which the bladder and rectum are affected provided that the lateral third of the parametrium is free.

Introduction of supraradical surgery was based on the observation that more than one-third of all uncured cervical carcinomas remain restricted to the true pelvis up to death. In the exenteration of the pelvis, all pelvic organs are usually extirpated (total exenteration). Exceptionally, the rectum and/or bladder can be left in (partial anterior and posterior exenteration). Performance of such operations requires great experience in visceral surgery and use of intensive-care measures. The technique and further details are to be found in the literature (*Kaeser* et al. 1973; *Mattingly* 1977; *Nelson* 1977; *Way* 1976).

Today, there is agreement that exenteration of the pelvis is indicated only when there is a prospect of cure. It is therefore not a palliative operation. The cases must be carefully selected and above all the risk of surgery and contraindications must be considered. The final decision on the feasibility of the operation can frequently only be made at exploratory laparotomy. This is indicated so long as distant metastases are not present.

The surgical risk of this operation increases with age. Women over 60–65 years old are not ideal candidates, especially when cardiovascular, renal, and pulmonary reserves are reduced. The risk of surgery is also influenced by adiposity. There is a correlation between the rate of complications and body weight. Especially dangerous is the condition after high-dose radiotherapy, since here the tendency to heal in the operation area is exceedingly poor. There may also be difficulties in psychological adaptation to the operation and its consequences, which are to be regarded as a contraindication for this operation. Preoperative preparation for stomata and their care is important.

A pelvic exenteration is contraindicated when the tumor has spread outside the true pelvis or cannot be removed. Ischialgia-like pain, progressive edema of the legs, and hydronephrosis speak against the resectability of the tumor. The presence as a resection level can only be established at laparotomy in many cases.

Further contraindications are preoperatively suspected or surgically demonstrated metastases of the abdominal organs, of the para-aortic lymph nodes as well as extensive lymph node metastases at the level of the common iliac artery. Invasion of the tumor through the peritoneum and cytologically demonstrated tumor cells in the peritoneal lavage are signs of generalization of the disease and should be regarded as a contraindication.

Choice of suitable cases, correct operation tactics, avoidance of technical errors, and careful postoperative monitoring and treatment are exceedingly important for prophylaxis and control of perioperative complications and for the result. At all events, this kind of surgery is associated with a high early and late morbidity. The most frequent complications are hemorrhages, shock, infection and sepsis, thromboembolism, and functional and anatomic disturbances of the gastrointestinal and urinary tracts. By improvement of the operation technique and introduction of some modifications, these complications have become rarer today.

The surgical mortality of local recurrences treated by hysterectomy was 2.5% and the 5-year survival rate 43% in the series published by *Barber* (1978). *Rutledge* et al. (1976) reports on the results of "radical" hysterectomy for persistence or relapse after complete radiotherapy. The 5-year survival rate is 55.3% (26 out of 47 patients). Of a total of 65 women operated on, fistulae of various kinds were observed in 16 (13 urinogenital and 3 rectovaginal fistuale). These figures point to the high morbidity of this operation after high-dose radiotherapy.

The 5-year survival rate after exenteration because of recurrent cervical carcinoma is between 25% and 30%. The figures of *Morley* et al. (1973) are impressive. They amounted to 70% or 80% when the regional lymph nodes were not affected. However, suitable cases for this operation are becoming rarer because of the improvement of radiotherapy. The following are to be mentioned as prognostically favorable factors: tumor-free pelvic lymph nodes, histologically carcinoma-free resection boundaries, the absence of extrapelvic metastases as well as young age and good general condition.

Table 5 gives information on the surgical mortality and the 5-year survival rate of pelvic exenteration in various hospitals. The quite acceptable surgical mortality and

Table 5. Surgical mortality and 5-year survival with pelvic exenteration [modified according to *Mattingly* (1977) and *Nelson* (1977)].

Author	Year	No. of patients	Mortality %	5-year survival
Dargent (France)	1957	83	31.3	26.0
Smith (NCI)	1963	71	8.4	15.5
Parsons (Boston)	1964	112	14.2	21.4
Brunschwig (New York)	1965	535	16.0	20.1
Rutledge (Houston)	1965	108	16.6	28.7
Kiselow (St. Louis)	1967	207[a] (54)[b]	7.8 (1.8)[b]	35.0
Symmonds (Mayo Clinic)	1968	118	12.0	26.0
Ketcham (NCI)	1970	162[c]	7.4	38.0
Brunschwig (New York)	1970	225	8.0	19.3
Symmonds (Mayo Clinic)	1975	198 (102)[d]	8.1 (3.0)[d]	33.0
Way (England)	1976	169	8.8 (1.5)[e]	26.4
Rutledge (Houston)	1977	296	13.5	42.1
Morley (Michigan)	1978	80	1.2	62.0

[a] 1950–1965

[b] 1960–1965

[c] 65 cases treated by primary exenteration

[d] 1963–1971

[e] 1970–1973

relatively high 5-year survival rate indicates that pelvic exenteration should be performed in suitable cases. By the improvement of stoma care and other rehabilitation measures, these patients are able to lead a normal life.

Surgical extirpation of isolated metastases can be indicated in exceptional cases. These are para-aortic or supraclavicular lymph node metastases or pulmonary and bone metastases, more rarely metastases to other locations (e.g., brain). Such operations with the aim of "cure" are only justifiable when a generalized disease has been excluded after careful diagnosis.

E. Surgical Procedures for Treatment of Complications and Side Effects of Primary Therapy

Side effects of various degrees of severity are frequent after surgical and/or radiotherapeutic treatment of cervical carcinoma, especially when operation and irradiation are combined. When one also takes into account the psychological burden and the impairment of sex life, any treatment of cervical carcinoma is associated with a high morbidity. In practice, only every fourth patient remains without somatic side effects after the operation. On the other hand, if only the severe complications requiring treatment are considered, the morbidity rate can be put at about 10%. However, precise figures are not known, especially on the late sequelae after radiotherapy. Prophylactic measures and refinement of the surgical technique and radiotherapy have doubtless led to a lowering of morbidity. However, the number of complications is still appreciable.

Surgical measures have great importance in the treatment of these complications. However, surgical therapy is very difficult. The following special features should be mentioned:

1. Establishment of the indication, choice of the surgical technique, and favorable timing are problematic;
2. Scars interfere with dissection and require great technical expertise, especially in radiation-induced alterations, in order to avoid incidental injuries;
3. The mortality of rehabilitation surgery is higher than that of the primary treatment in some operations;
4. Emergency operations are associated with a higher morbidity than the same kind of operation in visceral surgery.

For these reasons, both diagnostic clarification and treatment of such cases should only be performed in appropriately equipped centers. The technique of surgery must be chosen individually. One must frequently improvise, which requires appropriate surgical experience.

A large number of side effects occur after operation and radiotherapy of cervical carcinoma. Corresponding review papers are found in the literature (*Baltzer* et al. 1980; *Beck* 1979; *Castaño-Almendral* 1975; *Frischkorn* 1976; *Kaeser* et al. 1973; etc.). Only questions of sexual rehabilitation, complications of the intestinal tract, and the efferent urinary tract will be discussed here.

I. Sexual Rehabilitation

Today, this area is accorded more importance than formerly. *Reconstruction of the vagina* may become necessary after partial colpectomy, because of adhesions after radiotherapy or in association with exenteration. The choice of method and time of operation depends partly on the need of the patient, the prior disease and treatment, and the method by which the artificial vagina is formed. It must be taken into account that disturbance of sex life is only partially attributable to the anatomic alterations caused by the treatment. Psychological reactions to the disease both in the woman and her partner are likely to be more important. Thus in the woman, the castration syndrome in the wider sense, i.e. the feeling that the genital organs have been destroyed, plays a role. Libido and orgasm are impaired both primarily and secondarily by an anatomically induced dyspareunia. The partner avoids sexual contact partly because of fear of infecting himself with the carcinoma. These facts show that sexual rehabilitation is not exclusively an anatomic problem. Detailed explanation and sexual counseling are therefore of utmost importance.

Preservation of a vagina capable of functioning is being accorded increasing attention at the time of operation. The principle also applies here that one should operate as radically as necessary and with as much restraint as possible. If a more or less extensive vaginectomy is unavoidable, the defect can be bridged over with pelvic peritoneum. A vaginal tube of any desired length can be produced with peritonealization by the technique of Symmonds-Pratt. Adhesions and stenoses can be avoided by means of early spreading from about the 3rd to 5th postoperative day, repeated insertion of tampons with estrogen-containing ointments, insertion of a prosthesis if necessary, and initiation of intercourse about 6 weeks after the operation. A slight tendency to shrinkage will always remain, however. For this reason, some authors advocate primary lining with sigmoid tissue. Others prefer to cover the resulting wound with free epidermal flaps (*Lagasse* et al. 1978).

The problem of *vaginal reconstruction* after *high-dose radiotherapy* gives rise to more difficulties and the results are more unfavorable. The operation can be performed only after subsidence of the acute radiation reaction. Complete extirpation of the scar tissue, which is a requirement for succes, is difficult and sometimes impossible. The vaginal opening should be maximally stretched, possibly with indentation of the levators. The resulting lumen is lined with epidermal flaps and kept open with a prosthesis or loose-fitting tampon for about 7 days. The implant usually takes, but a more or less pronounced rigidity remains (*Watring* et al. 1976).

The problem of capacity for intercourse must be discussed with the patient and the partner before carrying out a pelvic exenteration, in order to plan the operation accordingly if necessary. The conventional methods for forming an artificial vagina in vaginal atresias are also used in these cases. *Morley* et al. (1973) line the wound cavity in the process of healing with epidermal flaps 6–8 weeks after exenteration, when the wound has roughly the size of a normal vagina. The flaps are laid on the granulation tissue and fixed with a loose-fitting tampon for about 1 week, after which the patient wears a prosthesis. Sexual intercourse should be commenced 2 months after the operation. The functional result of this method is satisfactory despite the tendency to shrinkage. Eventration of the small intestine through the perineal wounds is one of the

possible complications. *Pratt* (1966) reports on the reconstruction with a sigmoid segment. *McCraw* et al. (1976) have described a technique in which the vagina is formed from pediculate flaps of cutaneous muscle from the musculus gracilis during the operation.

After healing of the perineal wound and even years after the exenteration, the formation of a tube resembling a vagina can be produced if the patient wishes it by fusing the labia majora (operation according to Williams). Formation of an "internal" vagina is contraindicated in such cases. The possibility of coitus interfemora must be pointed out to the patient in case of failure or contraindications to the operations mentioned (*Way* 1976).

II. Intestinal Complications

Intestinal complications are more frequent after radiotherapy than after operation. They can be fatal. Intestinal complications due to radiation are more frequent even without taking mild cases into account and secondary changes occur more frequently than in the urinary tract. Proctitis and sigmoiditis due to radiation and the resulting sequelae head the list (*Mitchel* 1973; *Van Nagel* 1974).

Peritonitis and functional or mechanical *ileus* are treated in accordance with surgical principles. If these complications occur a long time after the primary treatment, one must consider the possibility of a recurrence and if necessary exclude this at laparotomy.

Colonic-vaginal fistulae are more frequently radiogenic than surgical in origin. In simple cases, a primary fistula closure can be attempted. Complicated cases require several procedures, namely (1) application of an anus praeter; (2) closure of the fistula after the inflammation has healed; and (3) relocation of the artificial anus.

Severe radiogenic *proctitis and sigmoiditis* which do not respond to conservative measures, recurrent persistent hemorrhages from the rectum, and narrowing of the intestinal lumen which impair intestinal function, as well as non-healing recurrent fistulae constitute indications for cecostomy. The possibility of a relocation must be considered here. Whether this is possible is decided according to the course of the disease and the result of the colon contrast enema and colonoscopy necessary before the reoperation.

Lesions of the small intestine occur after radiotherapy, extensive pelvic operations, or combined treatments. Small intestinal fistulae were formerly relatively frequent after exenterations because of the nonperitonealized pelvic cavity. This complication is rarely seen today with the new technique of pelvic lining. Chronic functional and organic alterations of the small intestine after irradiation have been observed frequently only since application of super volt radio therapy. They occur in connection with large irradiation fields and high tumor doses. Both apply in the irradiation of the paraaortic region. The patients complain of intermittent diarrhea alternating with constipation and weight loss: symptoms of malnutrition are likewise observed. A malabsorption syndrome can be demonstrated by appropriate function tests. Sometimes the symptoms increase to subileus or ileus. In terms of pathologic anatomy, the alterations

are very difficult to demonstrate and rarely correlate with the clinical symptoms. Proximal to the radiation-damaged region of the intestine, the intestinal wall is thin, the peristaltic movements are few, and the lumen is enlarged. Extensive desctruction of the mucosa or numerous micronodular filling defects, which are attributable to a radiogenic thickening and fibrosis of the submucosa can be observed (Fig. 6). However, radiologic changes which are very similar to those of Crohn's disease also occur. Occasionally, stenoses of varying extent can be demonstrated. Intestinal convolutions are also formed due to fibrotic adhesions and to shortening, thickening, and fibrosis of the mesentery. Radiogenic alterations of the intestinal vessels can be demonstrated by visceral (i.e., mesenteric) arteriography. It cannot yet be said with certainty whether this method is clinically suitable for differential diagnosis of further growth or tumor recurrence or irradiation sequelae.

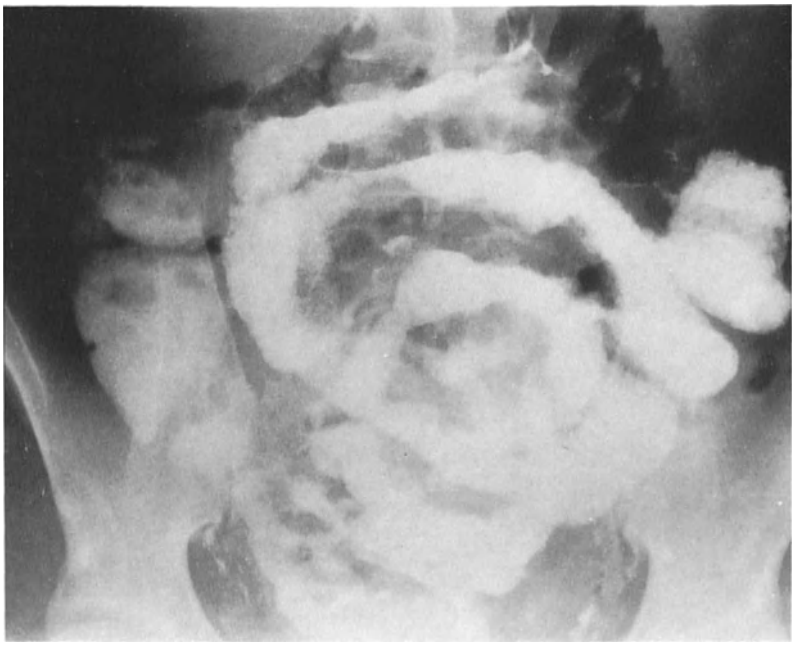

Fig. 6. Typical radiologic findings of the small intestine after radiotherapy

The *treatment* of these complications of small intestine is difficult and the success rate is low. Functional forms with a chronic course must be treated in cooperation with gastroenterologists. A recurrent subileus or an ileus which cannot be controlled by conservative measures as well as intestinal perforations and fistulae must be dealt with surgically. Bypass anastomoses and suturing of the perforation constitute the operations of choice. The disconnected and damaged small intestinal section is sewed onto the skin of the abdominal wall with formation of a mucocutaneous fistula. Freeing of adhesions or intestinal resections should be avoided because of the great danger of intestinal injuries and suture dehiscence. The mortality of these operations is high, around 30%. Repeat laparotomies cannot be avoided in about 20% (*Mitchel* 1973).

III. Complications of Efferent Urinary Tract

Functional and anatomic alterations of the efferent urinary tract are more frequent postoperatively than postradiologically. The *bladder* may be severely damaged by traumatization, severance of the ganglia of the inferior hypogastric plexus, scar formation, intravesical and perivesical infections, and in certain cases by postoperative irradiation. A certain prophylactic effect is achieved by: (1) avoiding radical resection of the vesicouterine and sacrouterine ligaments; (2) vacuum drainage to avoid accumulation of secretion and infection and the resulting perivesical scar formation; (3) prophylaxis and timely treatment of urinary infections; and (4) dispensing with unnecessary postoperative irradiation (*Kaeser* et al. 1973).

Various early and late complications occur as a result of this bladder damage and denervation. An early complication is the failure of spontaneous micturition to occur because of "sphincter rigidity." If conservative measures (repeated drawing off of urine and parasympathomimetics) are unseccessful, transurethral sphincter indentation is indicated when function is still disturbed 3 weeks after the operation. After extended hysterectomy, half of the patients still complain after years of inability to sense fulness of the bladder, of trouble in initiating micturition, of incomplete emptying, and of urinary incontinence. These micturition complaints are often intensified by frequently superimposed urinary infections which can in turn lead to a chronic pancystitis and to contracted bladder. These cases must be clarified urologically by urethrocystometry, urethrocystography, excretion urogram, and urinary sediment and bacteriologic investigation. Urodynamically, a detrusor hypertension is observed most frequently (in 52% of the cases); unfortunately, this can hardly be influenced therapeutically. On the other hand, treatment of compulsive micturition symptoms can be attempted with Buscopan. Stress incontinence with urodynamically demonstrated sphincter insufficiency without bladder dysfunction can be dealt with surgically. In such cases, we prefer a loop operation, with lyophilized dura. Urodynamically demonstrated additional detrusor dysfunction (usually hypertension) constitutes a contraindication for an incontinence operation despite irksome stress incontinence. Incontinence with residual urine formation and recurrent infections which cannot be influenced therapeutically may be an indication for intestinal conduit (*Gaudenz* 1977).

The pathogenesis of the radiation reaction and secondary conditions in the bladder have been compiled by *Ries* (1968). The early reactions are manifested clinically as cystitic symptoms. Superimposed bacterial infection is usually present. Exclusively radiogenic functional and anatomic changes in the bladder without additional infection are very rare (less than 5%). The irradiated bladder is always susceptible to infections, just as after an operation. Use of a urine antiseptic over a period of years is thus to be recommended. Macrohematuria occurring 2 years or later after the irradiation is mostly attributable to a secondary radiation reaction; it constitutes an indication for cystoscopic clarification. Fibrinolysis inhibitors administered locally or systemically have proved effective in hemorrhages from telangiectasias. Bladder instillations with proteolytic enzymes are indicated in ulcer coated with fibrin. Transurethral removal is indicated when calcium incrustations are present. The superimposed infection often present in these cases should be treated according to the antibiogram (*Ries* and *Ludwig*

1968). Bladder instillations with a mixture of vitamin A, pantothenate, corticoids, antifibrinolytics, and chemotherapeutics have good prospects of success in our experience. Partial resection of the bladder sometimes cannot be avoided in especially severe therapy-resistent or refractory recurrent cases (*Castaño-Almendral* 1975).

Routine performance of localization radiograms after each radium insertion and measurement of the radiation exposure of the rectum and bladder have made a decisive contribution to avoiding acute and severe radiation reactions of these organs. Fistula formation can be prevented if doses of 100 rads per hour, radiation exposures of 2000 rads per application, and total radiation exposures of 6000 rads divided into three applications are not exceeded. In addition, severe early radiation reactions are then very rarely observed. On the other hand, these measures have not contributed to a complete avoidance of late reactions (*Frischkorn* 1976; *Ries* 1969).

Urogenital fistulae after operation and/or radiotherapy must be operated on without delay after histologic exclusion of a recurrence. Precise localization of the fistula (bladder or ureter) requires cystoscopy and blue test, bladder filling with indigo carmine, and urogram; in addition, urine bacteriology and sediment analysis are necessary. Infections and inflammatory alterations must be treated preoperatively. Vesico-vaginal fistulae due to surgery should not be operated on before 6 weeks have elapsed, and radiation-induced fistulae, not before 6–12 months. Vaginal or transabdominal methods are chosen depending on the special features of the case. Makeshift operations cannot be avoided in radiation-induced fistulae. We prefer high colpocleisis (Latzko technique) for high vesiculo-vaginal fistulae after hysterectomy. Ureterovaginal fistulae should be operated on within 3 months after appearance, since otherwise there is a danger of loss of the kidneys. The operation of choice is a ureterocystoneostomy. In high fistulae with loss of ureter substance, the Boari procedure can be considered. Other operations, such as ureterostomy and ureter replacement by intestine, are rarely employed. See the literature for further details on surgical treatment of fistulae (*Lawson* 1978; *Kaeser* et al. 1973; *Mattingly* 1977; *Mayor* and *Zingg* 1973).

Complications of the upper urinary tract, mainly ureteric stenosis and its sequelae, have a complicated genesis. This may include direct effects on the ureter wall by operation or irradiation, impairment of ureteric function by edema and scar formation, and atrophic disorders resulting from altered vascularization due to operation or radiovasculopathy. Superimposed intracanalicular infections and functional and organic alterations due to the carcinoma itself or the prior operation play a role. These are thus mostly composite injuries. Ureteric lesions due exclusively to radiation are rare (about 5%). This clinical observation is consistent with results of experimental investigations in which it was observed that the ureter is relatively radioresistant. Ureteric stenoses after operations are more frequent than after radiotherapy. Irrespective of the pathogenesis, it must be taken into account that complications of the upper afferent urinary tract are relatively frequent and often have a clinically silent course. They can lead to the death of a patient who has been cured of the carcinoma in up to 10% of treated cervical carcinomas. For these reasons, regular monitoring of the upper urinary tract by means of chromocystoscopy, excretion urogram, and/or isotope nephrogram are of great importance in routine follow-up control. Pathologic findings here are more often due to recurrence than to the prior treatment. A recurrence must hence first be excluded by all possible means. Treatment of these cases requires close cooperation between gynecologists and urologists.

IV. Radiogenic Alterations of the Pelvic Organs

Severe radiogenic alterations of the pelvic organs can in exceptional cases be an indication for pelvic exenteration. These are recurrent combined fistula formations accompanied by pronounced fibrosis of the pelvic connective tissue ("frozen pelvis") and the "cloaca syndrome." The latter term is used to describe multiple fistulation accompanied by severe infection and necroses of the pelvic organs. If untreated, this complication often leads to death. In these indications, morbidity and mortality of exenteration surgery are especially high. In the series of *Spratt, Butcher,* and *Bricker* (1974), the mortality of the operation in radiogenic necroses was 23% (3 out of 13 patients). *Barber* (1978) carried out pelvic exenteration in 20 such cases. Only seven of these survived 5 years or more.

F. Surgical Procedures for Symptomatic Treatment

Symptoms which require surgical treatment can occur in incurable patients. The objective is to alleviate tormenting symptoms or to control potentially fatal acute complications. In accordance with the palliative character, only relatively low-risk surgical procedures should be employed. Furthermore, it must be considered whether prolongation of life is meaningful or whether it only unnecessarily prolongs the suffering of the patient. The indications should thus be established individually. Life expectancy, attitude of the patient and family, kind of complication, and type of operation necessary play an additional role. The most frequent symptoms are uremia, ileus, peritonitis, bleeding, and pain.

I. Postrenal Uremia

An incipient uremia or oliguria resulting from the walling around of the ureters by carcinoma tissue is actually a blessing for the patient, since the uremia death is regarded as "comfortable." In exceptional cases, one will decide on a unilateral ureterostomy and/or nephrostomy. Such interventions are hardly acceptable from a medical point of view. The prolongation of life is 3–5 months. On the other hand, an oliguria due to constriction or occlusion of the urethra by the tumor should always be treated. We prefer suprapubic drainage inserted under local anesthesia to transurethral catheterization. This can be left in without symptoms and without appreciable danger of infection for weeks. Application of a suprapubic bladder fistula can almost always be avoided in this way.

II. Ileus

Ileus symptoms due to narrowing of the distal region of the colon and sigmoid-rectal-vaginal fistulae constitute indications for colostomy. The use of transverse or sigmoid colon as anus depends on the location of the alteration and radiation sequelae in the skin and the intestine. The colostomy should also be located in an area which can easily be kept clean and is little altered by body movements. Such conditions are found in the right and left lower abdomen as well as in the middle between the navel and xiphoid process. We prefer primary opening to colostomy. Care of an aritificial anus generally does not give rise to any appreciable difficulties today (*Zenker* et al. 1975).

In isolated metastases of the intestinal tract which cause a mechanical ileus, various operations are necessary depending on their location, extent and number. Either partial resections of the intestine or diversion anastomoses compatible with palliation come in question.

III. Peritonitis

If peritonitis develops in patients with incurable, fully treated, histologically verified cervical carcinoma, surgical measures are contraindicated. The treatment is conservative and consists of aspiration of the small intestine by means of Miller-Abbot tube, infusion therapy, pain control, and possibly antibiotics.

IV. Hemorrhages

Hemorrhages from the tumor before the beginning of treatment and in recurrences are frequent complications. Seepage bleeding before primary treatment soon stops after intracavitary application of radioactive substances or after administration of a hemostyptic dose of about 1000 rads by percutaneous radiotherapy. Severe hemorrhages can usually be controlled by electrocoagulation, chemical cauterization (sodium nitrate, iron chloride, Negatol) and tampons soaked with antifibrinolytic substances. The surgical ligation of the internal iliac artery, necessary in exceptional cases, can be replaced today by pinpointed vascular *embolization.* The internal iliac arteries on both sides are located and probed with the angiographic catheter from the femoral artery under local anesthesia. Plastics injected through the catheter in a fluid or solid form produce lasting occlusion of the vessel (Fig. 7). Rapid hemostasis without an appreciable burden on the patient can thus be achieved. This procedure is also indicated in severe bladder hemorrhages due to tumor. Our own experience is very good and corresponds to that in the literature (*Wolf* 1979).

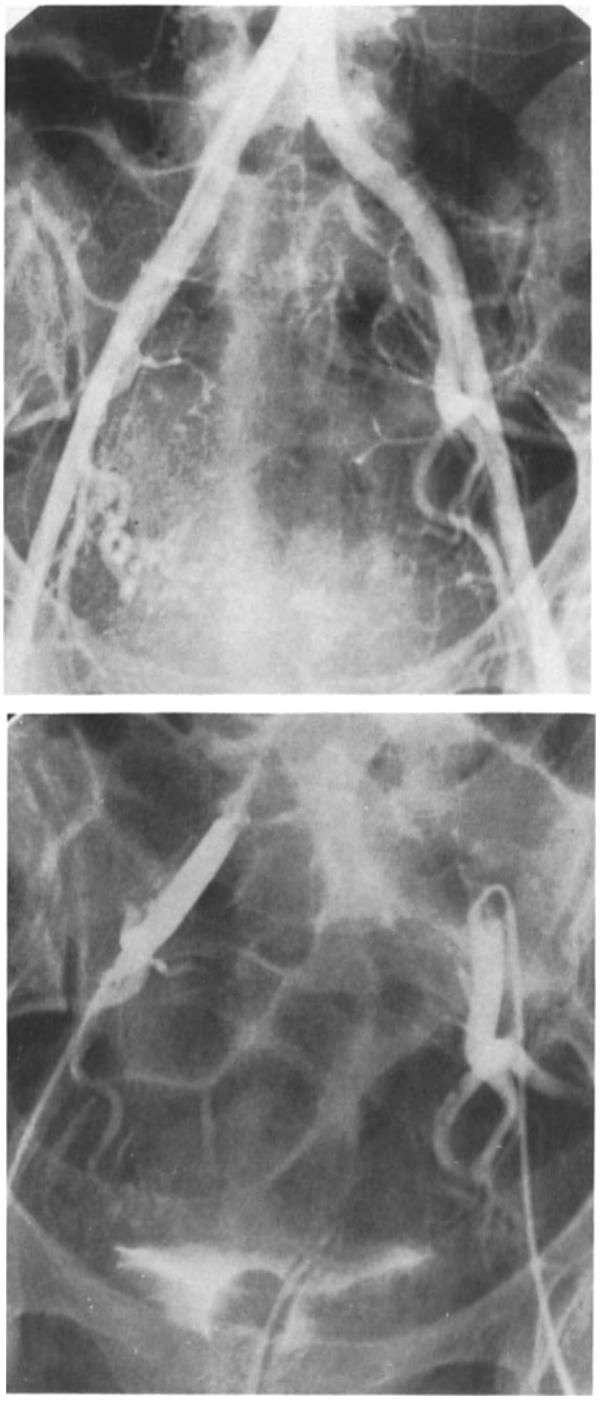

Fig. 7. Arteriography before and after embolization of the arteria iliaca interna

V. Pain

Pain is a frequent symptom in extensive incurable cases. Pain is a complex phenomenon: not only the pain stimulus, but also subjective pain sensation influence the quality and quantity of this symptom. The mental attitude to the disease and personality of the patient, belief and social environment determine the experience of pain in different ways (*Janzen* 1973).

Pain due to carcinoma has a highly complex genesis. Infiltration, irritation, and destruction of skin, subcutaneous tissue, fascia, periosteum, abdominal organs, blood vessels, peripheral nerves, plexus structures, and meninges (dura) are responsible for the pain due to the carcinoma. Patients with incurable cervical carcinoma complain above all of back pain, diffuse lower abdominal pain, and pain in the thighs. These symptoms are mostly due to infiltration of the femoral nerve, obturator nerve, and the sacral plexus. However, bone metastases or hydronephrosis must also be considered (*Leavens* 1972; *Lipton* 1977).

Surgical treatment of pain is fundamentally indicated when radiotherapy and chemotherapy are ineffective and control of pain by drugs is no longer possible.

Extirpation of bone metastases, operative treatment of pathologic fractures, and laminectomy with reduction of tumor masses are examples of surgical approaches. If the cause cannot be eliminated, techniques which interrupt the pain pathways can be considered. In principle, this interruption should be undertaken at the level of the primary neuron. Pain conduction can be interrupted by chemical substances (e.g., alcohol, hypertonic solutions, local anesthetics) or by neurosurgical intervention. The extent of the pain zone and the probability of further spread to other areas determine which technique should be applied. Neurosurgical interventions which can be considered are rhizotomy, cordotomy, mesencephalotomy, or possibly commissurotomy. In diffuse pain, intermittent electrostimulation of the thalamus, possibly combined with mesencephalotomy or cordotomy, give good results. Finally, in exceptional cases one of the so-called psychosurgical interventions such as prefrontal leucotomy or rostral cingulotomy can be considered (*Jenkner* 1977; *Mazars* et al. 1976; *Miller* 1972).

To summarize, pain control has become more successful and differentiated in recent years. The greatest advantage for the patient is achieved by close cooperation between gynecologists, neurologists, anesthetists, and neurosurgeons.

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Carcinoma of the Uterine Cervix - Radiotherapy

H.-L. KOTTMEIER

A. History

Radiation treatment of carcinoma of the cervix was initiated shortly after the discovery of roentgen rays and the radioactivity of polonium and radium. Gamma rays were first used in the treatment of cervical carcinoma because anatomically the uterus and vagina were appropriate areas for insertion of radium tubes. Moreover, the disease occurred often in young women and caused severe symptoms if not completely removed by radical surgery. Several techniques have been devised utilizing intracavitary radium therapy. Two basic methods have been used: The *Paris technique* delivers low-intensity radium irradiation over 120–130 h with daily removal and replacement after cleaning. Vaginal applicators made of cork are applied into the lateral fornices, and, when suitable, a third cork is placed between these. More recently, a moulded vaginal applicator has been designed for the individual patient. The size of the vaginal fornices and cervix, and the extent of the cancer are factors which are considered in the preparation of the mould. A plastic applicator is made with a thin layer of autopolymerized resin poured into the plaster. The radioactive sources are placed into the moulded plastic applicator. The radioactive tubes remain for 6 days and are not changed during this time. The patient can move and even walk. Antiseptic solution is applied every day. The *Stockholm technique* (Fig. 1) uses fractionated applications of rather high intensity. The aim of this method is to push the intrauterine tube up to the fundus and to cover the growth with suitable applicators of lead or Monel. As a rule, no radium is placed in the lower 1.5 cm of the cervical canal, except in some cases of endocervical lesions where the radium in the vagina is replaced by radium in the endocervix. The filtration is the equivalent of 2 mm lead. The amount of radium applied to the uterus varies according to the length of the cavity. As a rule, 68–74 mg radium is

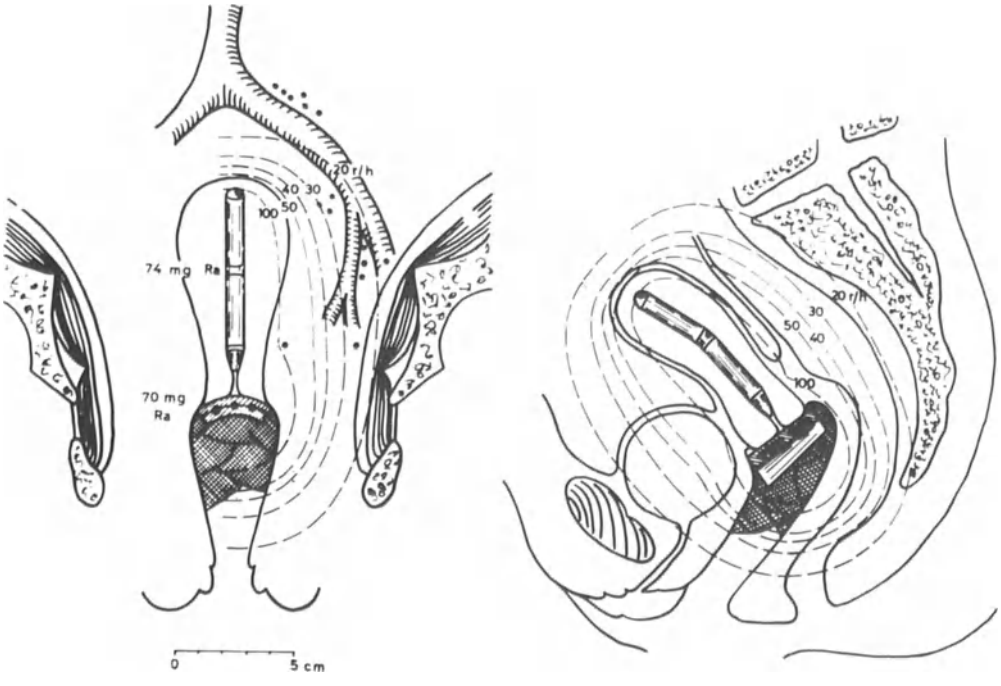

Fig. 1. Isodose curves. Stockholm technique

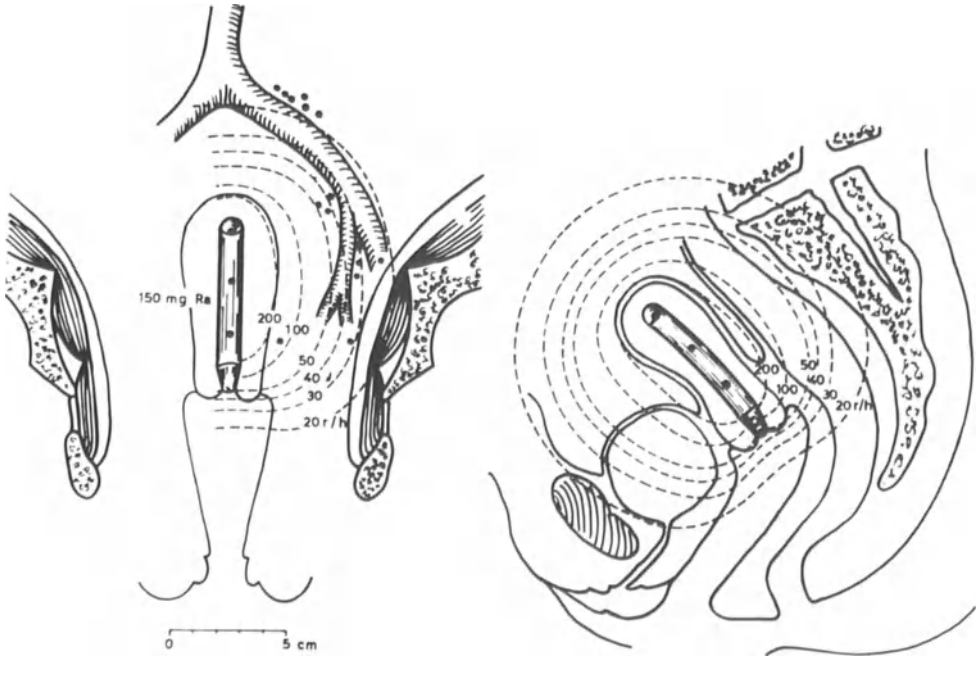

Fig. 2. Isodose curves. The radium is applied to a cancer in the posterior vagina wall

applied to the uterus and 70 mg to the vagina (Fig. 2). In cases of endocervical carcinoma, the amount of radium applied to the uterine cavity may increase to 150 mg (Fig. 3). The radium is left in situ for 20–30 h. The radiation is repeated after 3 weeks. In cases complicated by infection, treatment may be divided into three or more applications. A salpingectomy prior to radiation is done in cases of pyosalpinx.

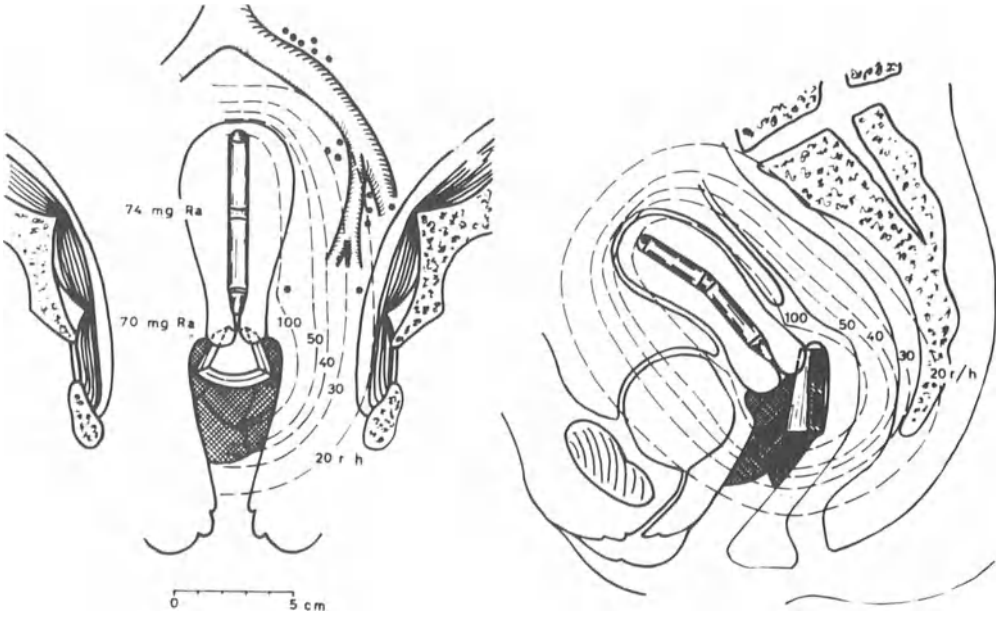

Fig. 3. Isodose curves from intrauterine radium in endocervical carcinoma

Several modifications in the techniques mentioned have been made. The frequently used *Manchester technique* is a modification of the Paris method. It makes use of two applications separated by 1 week. Each time the radium is left in place for 2 or 3 days. Two or three rubber ovoids are placed in the lateral fornices and against the growth. The significance of this method is that the type and size of the ovoids are chosen in such a way as to deliver a desirable dose to the paracervical triangle, indicated as point A by *Todd* and *Meredith* (1938) (Fig. 4). This point is located 2 cm lateral to the central canal of the uterus and 2 cm up from the lateral fornices in the axis of the uterus. A dose of 7000–8000 rad to point A from the radium was considered a suitable amount. *Fletcher* (1971) has modified the Manchester technique. His ovoids are easy to apply and have a diameter of 2, 2.5, and 3 cm. The ovoids have a handle which facilitates application and prevents them from slipping. *Fletcher* chose individual treatment in accordance with the Stockholm method.

Some radiotherapists are of the opinion that the applicator introduced into the uterine cavity should be attached to the vaginal applicator. The Stockholm method uses different vaginal applicators and a series of intrauterine tandem tubes. There is no mechanical connection between the two applicators; the purpose of this flexible sys-

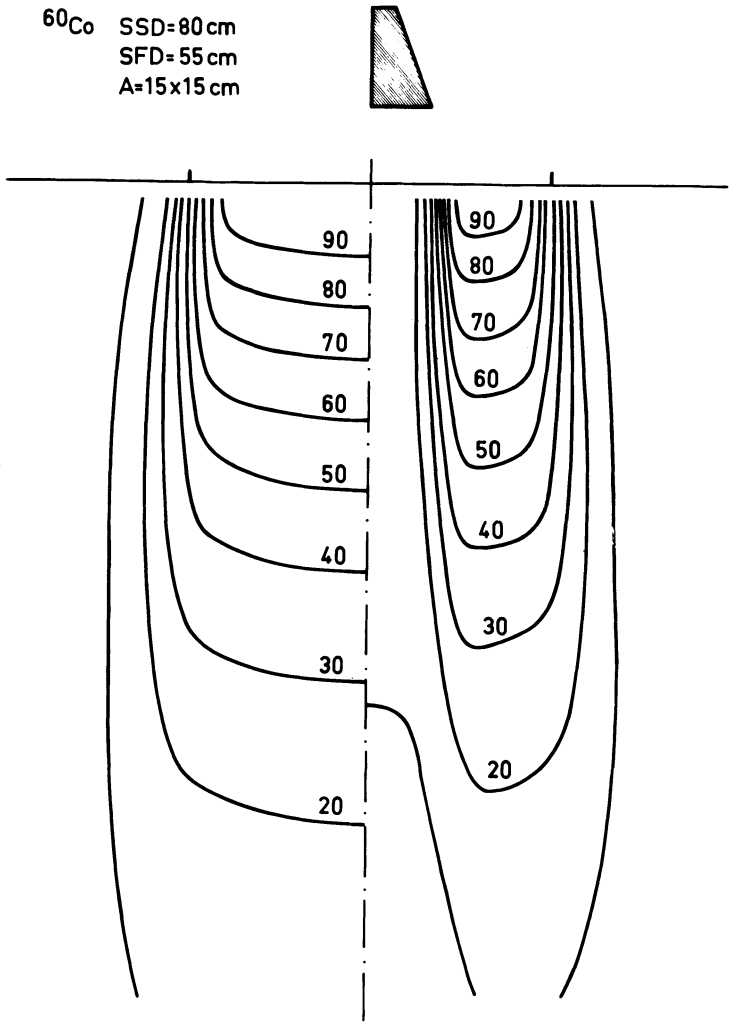

Fig. 4. Dosage distribution to Cobalt 60

tem is to cover the palpable extent of the tumor as completely as possible with a suitable combination of intrauterine and vaginal applicators. This also holds true for the Ernst applicator.

B. General Principles: Planning Therapy Physics

Radiation therapy for carcinoma of the cervix constitutes a combined treatment of external irradiation and intracavitary application of radioactive sources. Prior to the beginning of any type of radiation, a careful examination of the patient is carried out, preferably under anesthesia. This examination includes palpation and inspection, cyto-

scopy, biopsy, and curettage for histologic examination, as well as intravenous urography and roentgenography of the skeleton and lungs. In addition, it is desirable to do lymphangiography, although it is difficult to decide whether the findings are due to cancer. The anatomic extent of the neoplasm serves as the basis for a clinical staging. Clinical classification and staging is important. The presence of a hydronephrosis or a silent kidney due to the cancer will influence prognosis and therapy. Such findings would categorize the case as stage III. The facts mentioned serve as a basis of clinical staging, which is done at the beginning and cannot be changed even if, for instance, surgical exploration reveals metastases to regional lymph nodes. At present, a surgical staging does not exist. *Meigs* and *Brunschwig* (1952) proposed one, but it is unfortunately very complicated.

C. Definitions of the Different Clinical Stages in Carcinoma of the Cervix Uteri

Pre-invasive carcinoma

Stage 0 Carcinoma in situ, intra-epithelial carcinoma

Cases of Stage 0 should not be included in any therapeutic statistics for invasive carcinoma.

Invasive carcinoma

Stage I Carcinoma strictly confined to the cervix (extension to the corpus should be disregarded).

- Stage Ia Microinvasive carcinoma (early stromal invasion).
- Stage Ib All other cases of Stage I. Occult cancer should be marked "occ."

Stage II The carcinoma extends beyond the cervix, but has not extended on to the pelvic wall. The carcinoma involves the vagina, but not the lower third.

- Stage IIa No obvious parametrial involvement.
- Stage IIb Obvious parametrial involvement.

Stage III The carcinoma has extended on to the pelvic wall. On rectal examination there is no cancer-free space between the tumor and the pelvic wall.
The tumor involves the lower third of the vagina.
All cases with a hydro-nephrosis or non-functioning kidney.

- Stage IIIa No extension on to the pelvic wall.
- Stage IIIb Extension on to the pelvic wall and/or hydro-nephrosis or non-functioning kidney.

Stage IV The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum. A bullous oedema as such does not permit a case to be allotted to Stage IV.

- Stage IVa Spread of the growth to adjacent organs.
- Stage IVb Spread to distant organs.

In every case of carcinoma of the cervix, a planigram for radiation is taken in close collaboration with physicists trained in medical affairs. Silver clips are placed on the portio and the lowest part of the growth, and a metal probe is placed in the uterine cavity to establish the position of the uterus in the pelvis and its relation to the urinary bladder and the rectum. The anterior-posterior diameter is determined. Roentgenographs are taken. The contour of the patient's lower abdomen and pelvis is obtained by bending a piece of, for instance, foam rubber around the patient. The anterior-posterior dimension differs according to whether she is lying on her back or her abdomen. As a rule, the planigram is done through the center of the growth. It is frequently desirable to make two or three planigrams at the level of other parts of the tumor. Anatomic landmarks as well as the outline of the growth are indicated. The area of regional lymph nodes and the positions of the uterine corpus, the urinary bladder, and the rectum are indicated. Isodose curves for the sources applied to the uterus and vagina are available. This also holds true for the apparatus chosen for external radiotherapy.

Full information on the dosage distribution in three dimensions can be obtained with the help of a computer. A complete dosimetry is given. From clinical point of view, such an examination is complicated. However, it is still possible to ascertain the dose at several points, which is of considerable value for individual radiation. This is a distinct improvement compared to restricting the information of the dose to points A and B. Point B is on the same level as point A, 5 cm from the midline (Fig. 4).

The fields for the external radiation are marked on the skin of the patient. The control and modification of the fields are carried out with the simulator. Attention is given to the position of the uterus. If the uterus is drawn over to the right or the left side of the pelvis, it is necessary to be aware of the isodose curves from the radioactive sources in the uterus and vagina. Attention must be paid to the uterus position in order to give a homogeneous dose in the total pelvis. If this has not been considered, the radiation may cause overdosage in one parametrium and underdosage in the parametrium on the other side. Dose rate measurements in the bladder and rectum were introduced some 25 years ago. The Siemens cadmium sulphide gammameter is appropriate for direct measurement of the dose. Measurements are carried out with a stiff, curved probe with centimeter markings and are made at a number of points along the rectal and bladder walls. An average of the three consecutive highest values along these measured areas is considered to be relevant in the event of a late reaction. Since the position of the patient influences the dose, it is desirable to perform the measurements quickly, with the patient in a lithotomy position. The dose in the rectum may increase by 25% over a period of 24 h. This increase can be the result of maceration of the gauze packing used to keep the applicators in position. Thus, the measurements serve to control the position of the sources applied to the uterus and vagina. The average dose in an area of 3 cm serves to determine the amount of time the radium will stay in situ. Indeed, it is impossible to give any figures for determining the appropriate dose in the bladder and rectum. Each institution must work out representative figures. At the Radiumhemmet, 65–80 mg radium is inserted into the uterine cavity and 70–80 mg into the vagina. As mentioned above, the treatment is given twice, about 3 weeks apart. The dose for clinical use is 4500 rad in the rectum and 5000 rad in the urinary bladder.

Opinions differ concerning the number of radium insertions and the treatment time. The Manchester technique recommends two applications with an interval of 1 week. *Fletcher* (1971) divides radium therapy into two applications not less than 2 weeks apart. *Graham* and *Graham* (1953, 1955) studied malignant and benign vaginal cells in smears taken in the course of therapy. They claimed that destructive changes in benign cells are related to radiocurability and believed that the presence of many destructive benign cells seems to be a sign of good radiocurability. Later studies do not confirm these observations. However, one fact remains: Benign cells recover 2.5–3 weeks after the first treatment, while malignant cells show no sign of recovery within this period. The Radiumhemmet's practice of having a 3-week interval between applications is in accordance with this observation.

External irradition has become more and more important since the development of machines which permit a satisfactory dosage distribution. At the time when only orthovoltage roentgen treatment was available, it was impossible to give a desirable dose to the parametrium and regional pelvic lymph nodes. It is remarkable that even in those years good results were obtained in many cases, which supports the theory that oxygen tension varies considerably in different parts of the parametrium. Consequently, it is likely that a homogeneous dose to the pelvis is not always desirable. Some therapists have tried to give exclusively external irradiation. Personally, I am convinced that intracavitary radiation should be applied and should be individualized.

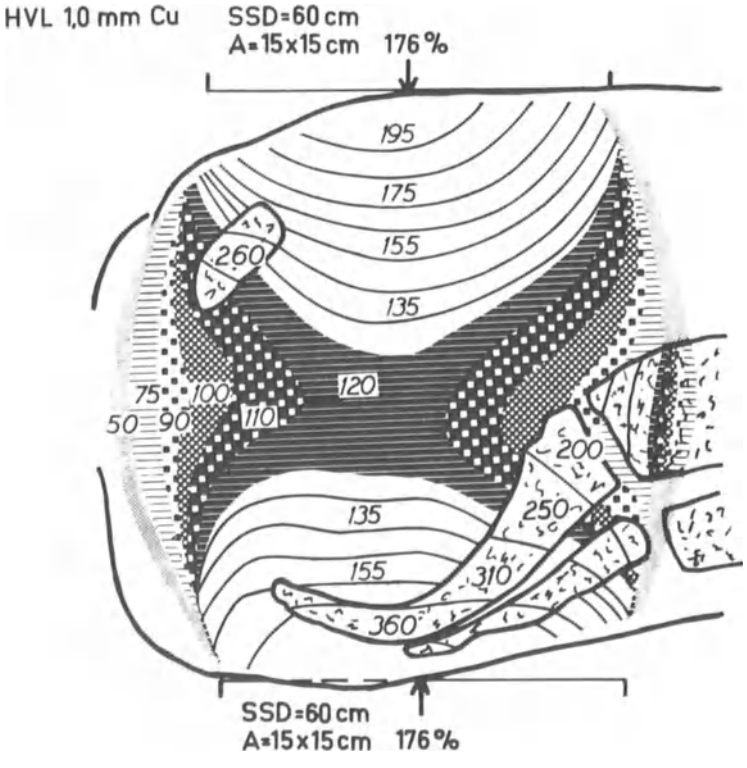

Fig. 5. Dosage distribution from linear accelerator 6 MeV

External radiotherapy can be delivered by a megavoltage machine, by telecobalt 60 gamma rays (Fig. 5), a linear accelerator, a betatron, etc. The Radiumhemmet has facilities to treat cancer of the cervix with a 6 or 8 MeV linear accelerator or a 42 MeV betatron. The radiation is carefully planned. Most patients are treated with the linear accelerator; obese patients receive gamma rays from the betatron. Telecobalt 60 was used long before better facilities were available (Fig. 6).

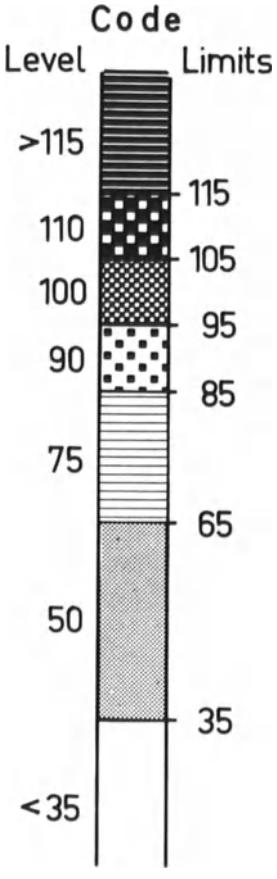

Fig. 6. Isodose curves. Cobalt 60 with or without shielding

The radiation is delivered from two opposing anterior and posterior portals or sometimes from four ports (Fig. 7). In the years, when telecobalt was given, lateral fields were used. Special absorbers of lead are used to protect areas which have received large doses from, for instance, radium applied to the intracavity. These absorbers are 25, 50, or 75 mm high and 30 mm wide. The correct place of the absorber is controlled by the simulator or by roentgen films. The external irradiation includes the whole pelvis up to the lower border of the fourth lumbar vertebra (Fig. 8).

A suitable dose is 800 rads given for 5 days. The dosage locally applied depends on the age and condition of the patient, the extent of the growth, the primary reaction,

and the dosage distribution from the radium (Fig. 9). The total dose varies from 4000 –5000 rad.

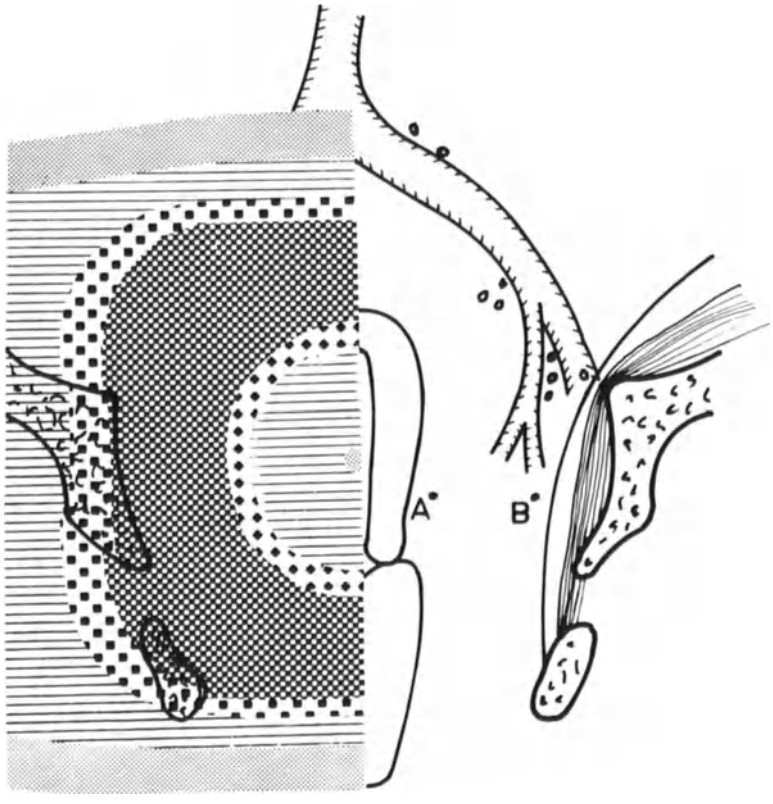

Fig. 7. Radiation treatment of the pelvis with anterior and posterior ports

In recent years, substitutes for radium have been developed. Iridium 192 and Cobalt 60 have disadvantages, particularly because of their short half-life. The half-life of cesium 137 is 33 years and the energy of gammaradiation is 0.66 MeV. This isotope has advantages over radium and will be used more frequently in gynecology. The dosimetry of cesium is identical physically and radiologically to that of radium.

D. Pathology

The great majority of cervical carcinomas are squamous cell cancers. A careful investigation of the size of the cells and the cell configuration and arrangement by *Reagan* et al. (1957) is of interest. They divide the cases into three groups with regard to cell differentiation and size. Group I includes relatively well differentiated, large-cell keratinizing cancers. Group III is made up of small-cell cancers without evidence of keratinization. Group II cases have rather larger cancer cells with unusual keratiniza-

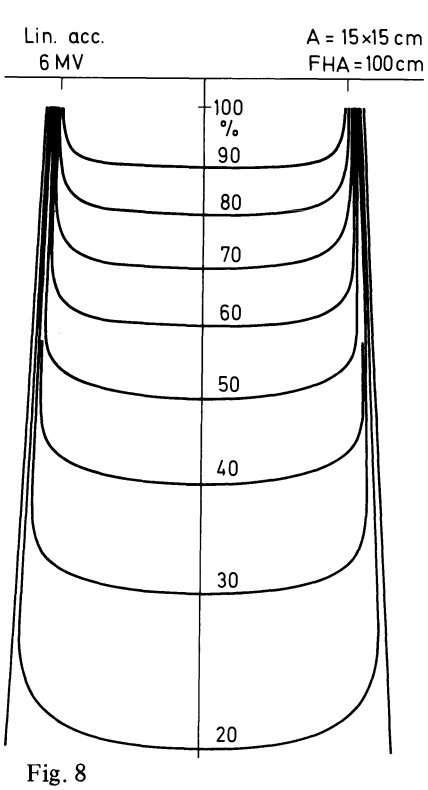

Fig. 8

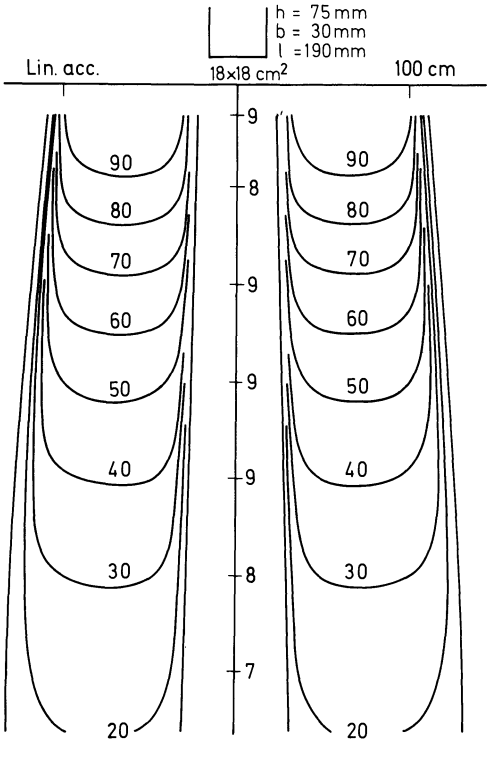

Fig. 9

Fig. 8. Dosage distribution from linear accelerator with absorber

Fig. 9. Code for the dosage distribution

tion. Opinions differ concerning radiosensitivity and radiocurability of the cancers in the three groups. As a rule, cases of small-cell cancers have a poor prognosis.

Adenocarcinoma and adenoacanthoma amount to 5%–10% of primary carcinomas of the cervix. It is often impossible to tell whether the growth has emanated from the ectocervix or from the endocervix. Radiotherapists previously considered adenocarcinoma of the uterine cervix to be radioresistant. Experience has shown, however, that cases of adenocarcinoma respond to radiation in the same way as epidermoid carcinoma. Some authors believe that metastases to regional lymph nodes are more common in cases of adenocarcinoma than in cases of squamous cell carcinoma. A special type of adenocarcinoma with mucin-producing areas has been observed. *Glücksman* et al. (1964) have collected a series of such cases. This type of growth as well as rare cases of adenosquamous cancer have a poor prognosis.

A brief outline of several factors involved in radiotherapy for treatment of cervical carcinoma has indicated that satisfactory results can be obtained only if treatment is done by skilled radiotherapists with experience in gynecology.

The endometrium and myometrium of the uterus tolerate immensely high doses. The depth dose from the uterine tandem and the applicators in the vagina decreases rapidly in accordance with the inverse square law. Consequently, the dose is unsatis-

factory when applied to the pelvic wall 5–7 cm from the midline. Radium applied to the uterine cavity has a greater influence on the dose in the endocervix and paracervical tissue, but this does not hold true for the paravaginal tissue. As a consequence, it is desirable to have applicators which permit a modified application of radium.

E. Treatment Policies

Stage Ia (microinvasive carcinoma)
Since metastases to regional lymph nodes are rare, treatment can be restricted to intracavitary application of radium.
Stage Ib
Intrauterine and intravaginal radiation is given primarily in cases of disc-shaped tumors and good local anatomy. Radium is applied twice to the uterus and vagina 3 weeks apart, followed by external irradiation to the parametrium and regional lymph nodes. About 7000 milligram-hour (mgh) is given. A dose of 4000 rad is delivered by external radiation. No radium is applied to the lower 1.5–2 cm of the uterine canal. However, in cases of endocervical cancer it is convenient to apply radium to the external os, thereby decreasing the dose of radium applied to the vagina. In cases of exophytic lesions, irregular tumors, and narrow vault, treatment starts with whole-pelvis irradiation. A dose of 3000 rad is given in 3–4 weeks. A repeated examination is performed and it is likely that radium can be inserted. A full dose of external radiation can cause shrinkage, not only of the tumor, but also of the vaults, thereby rendering a satisfactory application difficult. External radiation will continue later up to a total dose of 4000–4500 rad.
Stage IIa
Irradiation corresponds to therapy in cases of stage Ib.
Stage IIb
Whole-pelvis irradiation in a dose of 4000–4500 rad is given, followed by intracavitary application of radioactive sources. It is sometimes desirable to interrupt external radiation after 3–4 weeks.
Stages IIIa and IIIb
Therapy starts with external radiation through one anterior and one posterior port; 5000 rads are given over 6 weeks, followed by one intracavitary radiation with 5500–7000 mgh radium.
Stage IV
Whole-pelvis irradiation is given with 7000 rads. Frequently the radiation is intended to be palliative. However, to achieve a good palliation it is necessary to give at least 4000 rads.

In cases of suspicious paraaortic lymph glands, radiation can be applied to an area covering the paraaortic nodes and the aorta. The area is 25–28 cm high and 8 cm wide.

Opinions differ concerning the healing process of a cervical carcinoma treated by radiation. Great variations exist in this respect. Tumors which respond rapidly to radium have a poor prognosis as, in my experience, distant metastases are rather common.

The presence of malignant cells in smears and biopsies 6 months or more after radiotherapy is sometimes a sign of recurrence. Provided the primary treatment was satisfactory, it is unlikely that further radiation will be necessary. Surgery may be attempted, although the risk of complications is high.

F. Results of Therapy

The Annual Report on the Results of Treatment in Gynecological Cancer (1979) gives 5-year survival rates. In 1958 the International Federation of Gynecology and Obstetrics assumed the patronage of the Annual Report. The latest report appeared in 1976. It presents 61 146 cases treated from 1964–1968 and the survival rate 5 years after treatment was 55.5%. For 18 440 cases of stage I, the 5-year survival rate was 80.4%; for 22 482 cases of stage II, 58.9%; for 17 290 cases of stage III, 32.8%; and for 2934 cases of stage IV, 7.1%. Twenty-three institutions report on at least 200 cases in both stages I and II. An investigation of this material shows that no significant changes are registered in stage I between surgery and radiotherapy. For stage II it seems that the results are slightly better after radiotherapy.

At the Radiumhemmet, 925 cases were treated in the years 1969–1972. The 5-year survival rates are shown in Table 1.

With regard to carcinoma of the cervix, recurrences more than 5 years after therapy are comparatively rare, but since they may occur, examining the patients is desirable for at least 10 years. At the Radiumhemmet we have seen recurrences in 5% of cases which were symptom-free at 5 years.

G. Complications from Radiotherapy

Irradiation in cases of carcinoma of the cervix causes complications, particularly in the skin and subcutaneous tissue, the bowel and especially the rectum, the urinary bladder, and the ureters. A clinical grading system has been established to describe reactions and complications in the urinrary bladder and rectum.

Urinary reactions:

Grade 1	Subjective symptoms, i.e., mild
	Objective symptoms, i.e., minimal
Grade 2	Necrosis, pain, or hemorrhage requiring treatment and blood transfusion
Grade 3	Fistula

Rectal reactions:

Grade 1	Subjective symptoms, i.e., mild
	Objective symptoms, i.e., minimal
Grade 2	Necrosis or ulcers
Grade 3	Rectal stenosis requiring colostomy
Grade 4	Fistula

Table 1. Cases of carcinoma of the cervix treated at the Radiumhemmet 1969–1972[a]

	Number treated		%		Number 5-year survivals		%		Died "cervical cancer"	Died "intercurrent disease"	Lost to follow-up
Stage Ia	88 (14)	345 (60)	9.5	37.3	85 (13)	303 (59)	96.6	87.8	0	3 (1)	0
Stage Ib	257 (46)		27.8		218 (46)		84.8		27	12	0
Stage IIa	207 (18)	389 (21)	22.4	42.1	146 (11)	228 (14)	70.5	58.6	50 (6)	11(1)	0
Stage IIb	182 (3)		19.7		82		45.1		84	15	1
Stage III	128		13.8		34		26.6		86	8	0
Stage IV	63		6.8		8		12.7		52	3	0
Total	925 (81)				573 (73)		61.9		299 (6)	52 (2)	1

[a] Numbers in parentheses indicate patients who underwent major surgical intervention.

Grade 1, bladder and rectal, cannot be considered a complication. The symptoms are mild and are experienced by many patients, as is diarrhea. In cases of frequent evacuation of the bowels, it is desirable to interrupt radiation for several days. Complications in the rectum (tenesmus, hemorrhage, pain) begin 6–12 months after radiation. Injuries to the bladder (necrosis, hemorrhage) appear later and have been observed many years after primary treatment. Severe complications requiring surgical intervention have been observed in 1–2% of the cases. Injuries to the bladder and rectum are due to overdosage and can be avoided through careful planning of therapy.

Complications due to radiation require various treatments. In cases of stenosis of the rectum or sigmoid and of fistula, a colostomy of the sigmoid or large bowel is performed. A resection of the bowel is not appropriate. In cases of severe necrosis of the bladder, local application of cortisone is of value. Fistula of the urinary bladder is a serious complication and an operation to repair it is of no use.

Primary radical hysterectomy is done by gynecologists in cases of stages I and IIa. Opinions differ as to whether postoperative irradiation is of value. External radiotherapy is done in cases with positive nodes. Some therapists prefer to apply radium to the top of the vagina.

Stallworthy (1964) and some other surgeons have recommended starting therapy in stages Ib and IIa with intracavitary radium. A radical hysterectomy is carried out 3–4 weeks later. As a consequence of the radiation, the dissection is easy and the risk of postoperative complications small. External radiotherapy may be given later but is not indicated prior to surgery. In recent years this method has been adopted at the Radiumhemmet in patients 50 years of age or younger and has been performed on 132 patients 20–44 years of age. The 5-year survival rate is 89.9% in stage Ib and 76.8% in stage IIa. Complications following therapy are uncommon.

H. Radiation Protection

Radiation exposure in intracavitary treatment of carcinoma of the cervix is a problem for the staff both at the operating theater and in the ward. Staff duties include handling the sources to the uterine cavity and vagina, transporting the patient from the theater to the ward, and supervising the patient. Various steps have been taken to decrease exposure to the staff, but it is still difficult to avoid. Afterloading in curietherapy has been proposed. Three types of afterloading have been submitted for consideration: intraoperative afterloading, postoperative afterloading, and remote afterloading. A manual of afterloading techniques was proposed by *Henschke* (1960) and has been used by many radiotherapists in recent years, for instance in Paris. The sources are introduced into empty containers applied to the tumors. In remote afterloading the sources are inserted into the patient in a special shielded room from an outside control stand. Indeed, this method decreases exposure to a minimum. Special remote-control apparatuses have been proposed. The first special intracavitary remote-control apparatus was built by *Kottmeier* and *Walstam* in 1963. A second version used small Cs 137 sources in stainless steel capsules 3 mm in outer diameter and 8 mm long. This machine is called a Cervitron. Further improvements have been made, but it is

still in the development stage. This holds true both for the use of suitable sources and for improvement of the machine so that problems for the patient will be minimized.

Most radiotherapists have used low-dose rate techniques during afterloading, but others have tried high-dose rate techniques.

In the United Kingdom, the Cathetron system has been applied using Co 60. Application of the sources is done under anesthesia. The radiation is fractionated, with each application lasting 5–10 min. Manchester ovoids are used, and the dose applied varies. Good results have been obtained, and it seems that the use of the Cathetron is promising.

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