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*Modern Trends*

*Volume*

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Edited by

R. J. KELLAR

# MODERN TRENDS IN GYNAECOLOGY

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R. J. KELLAR

M.B.E., F.R.C.S., F.R.C.P., F.R.C.O.G.

*Professor of Obstetrics and Gynaecology, University of Edinburgh*



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# FOREWORD

This book is a companion volume to *Modern Trends in Obstetrics*. The publishers having thought it desirable to alter the format of the series to a smaller size it was necessary for the two subjects, previously published together, to appear independently. It is the intention that these volumes will be published at more frequent intervals than the previous *Modern Trends in Obstetrics and Gynaecology* series edited by the late Mr. Kenneth Bowes.

The selection of subjects for this volume has been a difficult task but it is hoped that a sufficiently representative number of modern trends has been included.

I wish to thank all the authors for the care with which they prepared their contributions, and also the staff of Butterworths for their help in the production of this book.

ROBERT KELLAR

*Edinburgh,*
*April, 1963*

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CHAPTER 1

# NON-INVASIVE CERVICAL CARCINOMA— PROBLEMS OF DIAGNOSIS AND TREATMENT

A. F. ANDERSON

The study of non-invasive cervical carcinoma presupposes that it can be defined, and certainly there must be some communicable description of it so that we may attempt comparison of the management of the lesion with that in other centres than our own.

## DEFINITION

There are those who hanker after true invasion before they use the word cancer at all, and there are a few who would include in the ' non-invasive ' stage, changes of de-differentiation occupying far less than the full epithelial thickness. Common sense has now led most of those studying this problem to accept the lesion as malignant, and the same common sense concludes that there must be all quantitative and qualitative degrees of malignant change from the first few identifiable cells, to the frankly invasive growth which is clinically visible. Between these two extremes we have the non-invasive cancer which is accepted as cancer but shows no invasion of the tissue below the epithelium. ' Intra-epithelial ', *in situ* and *pre-invasive*, are other terms commonly used, but the first two are unduly clumsy as well as obscure, while the latter implies that invasion is to be expected at some future time, which is not necessarily the case. The term ' pre-cancerous ' should be avoided both because it implies eventual invasion, and because we do believe that the lesion is already cancerous. The most reasonable description is probably ' non-invasive squamous cancer ' as argued by Morton (1957) (the term ' clinically benign ' is at all times misleading).

The most acceptable definition of this lesion is that the full thickness of the squamous epithelium should show cells with malignant characteristics giving the whole integument a malignant pattern. This definition accepts what is true for all histological descriptions, that there must be a large subjective element about the final decision; let it be called a personal element to be quite clear, but let it be admitted that this also affects accepted invasive malignancy

in many parts of the body, and must be a factor to be taken into account more and more as the size of the lesion diminishes below what can be seen by the naked eye. Those pathologists who demand ' stricter ' or ' more clearly defined ' descriptions of the lesion are not realistic and are not keeping the door open to bettering the plight of the most important single being in this study—the patient. As pathologists, we all become stricter with experience, and nothing else can take its place.

## DESCRIPTION

The simple statement that non-invasive cervical carcinoma is identical with squamous cancerous epithelium but without invasion is sufficient description for those who have become familiar histologically with squamous cancer *with* invasion. But for the increasing number of gynaecologists and pathologists who find they must study this problem it is probably helpful to describe the appearance of non-invasive cancer, and certainly it should be helpful to those so mesmerized by the ' apparent invasion ' of squamous metaplasia as to describe it as malignant, without studying the type of epithelium. The late Emil Novak constantly warned us of the danger of this and the inevitable overtreatment naturally carried out as a result.

Cancerous squamous epithelium can be described from two aspects—that of the separate individual cells and that of their pattern from basal cell layer to the surface during normal differentiation.

### Individual Cells

The individual cells show chiefly the malignant characteristics outlined so well for us nowadays by cytologists, though some of the features are diminished by the shrinking and closer packing caused by the preparation of the paraffin block. Hyperchromatism, variation in staining, size, and shape of the nucleus—especially the shape, dense nuclear outlines and normal and abnormal mitotic figures—all contribute to a recognizable picture, as in a cytologist's smear. The increased proportion of nuclear size to cell size, or the nuclear-cytoplasmic ratio, is naturally not so well seen as in wet fixed smears of fresh cells, but it is still important and may be evident and helpful. These changes, as in cytology, are chiefly nuclear and it is to the nucleus we must look to differentiate the lesion from benign squamous metaplasia, where the nuclear shape is largely circular or oval and not irregular.

## Pattern of Cells from Basal Layer to Surface

The pattern of these aberrant cells from basal cell layer to the surface may show complete loss of polarity or differentiation, so that it would look the same upside down, or there may be variable hints of differentiation here and there with some flattening of the surface cells though these are still recognizably aberrant. It is plain that there must be all degrees of loss of differentiation, or loss of polarity, or all degrees of anaplasia, and this is why most writers have accepted these changes in the ' full thickness ' of the epithelium, as a criterion for the *extent* of the pattern of malignancy. We may logically reason that there must be stages before this ' full thickness ' appearance has developed, but to introduce fractional degrees would increase enormously the subjective element in what is already a very subjective impression. It is thus believed to be more advisable to describe these changes occupying less than the full thickness as ' basal anaplasia ' or ' borderline ' malignant changes, implying practically, as this does, that the lesion has been discovered at a stage earlier than the full thickness, with consequent improvement in the prognosis (Te Linde, 1956).

## Problem of Future Development

The chief problem with atypical lesions occupying *less* than the full thickness of the epithelium is really the same as with the fully developed non-invasive cancer, namely their possible future development towards acceptable neoplasia. The chances of non-invasive cancer becoming invasive are still not clear but there are few now who deny its dire potentiality. Hertig (1957) pointed out, and this must be for ever remembered, that with such minute malignant areas as we are now able to discover, there is an eternal dilemma where, on the one hand, we remove the entire lesion with a biopsy designed to be large enough to find it, and on the other, we take smaller, or punch biopsies, with the chance of missing the lesion altogether, or missing an invasive area of it. It is admitted that both methods are practised with probably the same benefit to our patients, whose interests may not always be put first in attempts to demonstrate ' scientifically ' the natural history of these small lesions. With the methods of cytology, colposcopy and biopsy, with ever-continued observation over years, we come as close as we can to knowing what happens once the initial malignant change has been discovered and we know that there are many latent years of growth to comfort us if definitive treatment is not immediately undertaken. However, the words ' scientific ' and ' proof ' are still too frequently used for a problem

with the inherent dilemma that the means of diagnosis may also constitute complete treatment.

## Methods of Observing the Natural History of the Lesion

The methods of observing the natural history of the lesion need only be referred to briefly for their drawbacks to be quite evident, though the major trouble is the subjective element in the original diagnosis of the lesion, which exists for much larger and more obvious growths in other regions whenever many pathologists are requested to give opinions on the same lesion. This was excellently demonstrated by Siegler for the cervical lesion (Siegler, 1956). The observation of diagnosed cases left untreated to discover what proportion becomes invasive, is open to the possible contradiction in terms of the phrase 'diagnosed but left untreated' as explained above; we cannot be scientifically certain of this situation! The famous series of Kottmeier (1953) and Petersen (1956), widely quoted, are open to this criticism, and Kottmeier is the first to agree that some of his cases may have been invasive when initially discovered. Petersen's series is a little more striking but because of the weight attached to it, sorely cries out for independent scrutiny of the histological slides.

Another method of observing the lesion is the retrospective method of searching the previous records of those diagnosed with incontrovertible Stage I to Stage IV cancers, as has been so ably done by Galvin, Jones and Te Linde (1952). This approach, discovering many more cases with previous biopsies in which non-invasive lesions had been missed than could be attributable to chance, is enough for most of us, again putting the interests of our patients first (and indeed has been used by Hertig and Sommers in the study of the early stages of fundal adenocarcinoma). Yet there are still some who will not acknowledge that, by this approach, we have any evidence worthy of attention.

The most recent, and surely the most significant statistics of all, however, relate to the lowering of the incidence of clinically visible and invasive cancers in regions where facilities exist for winnowing out the non-invasive lesions by cytological screening 5–10 years earlier. This has now been done superbly by Boyes, Fidler and Lock (1961) showing a drop in the incidence of clinical cancer from 28 to 19 per 100,000 over 10 years. This work only awaits repetition by the same group over another period of years, or confirmation by any other centre with equal facilities. A similar suggestion comes from Yule (1961) who found an increase in the actual number of deaths from cervical cancers in Scotland during the last 10 years, except in

Edinburgh and Dumfries where there was a drop and where by far the bulk of cytological screening of gynaecological patients in Scotland is carried out. Meigs (1956), also, has noted that the number of invasive cancers is decreasing in Massachusetts as a result of increasing treatment of *in situ* lesions.

There must be few now involved in these problems who have not experienced the eventual demonstration of invasion where the original lesion, possibly years earlier, seemed to be non-invasive. This is all we need to institute close diagnostic observation at the very least, and it is refreshing to know that such a noted pathologist as Fred Stewart (1957) of the Memorial Hospital in New York has gone so far as to say that ' every infiltrative cancer must come from *in situ* cancer, there being no other thing it can come from, this irrespective of various doubts cast upon the relationship '.

## Relationship of Non-invasive Cancer to Less than Full Thickness Atypical Changes

With this brief review of the present situation as regards non-invasive cancer, what is its relationship to the atypical changes occupying less than the full thickness? There are probably only three points worth much weight at the moment, but the weight is considerable. These changes have been styled by as many titles as has non-invasive cancer. ' Basal atypism ' and ' basal anaplasia ', being the most informative, and carrying some warning to the clinician, though Emerson Day recognizes both minor and major ' atypical lesions ' both short of unequivocal non-invasive cancer, and ' atypical hyperplasia ' and ' dysplasia ' are also in current usage. Excellent illustrative photographs of all grades of change have been published by McKay and colleagues (1959) and should be seen by all those beginning their experience at the present time. McKay's paper also brings out the first point worth making in the relationship of the two lesions. This is that, as discovered by screening procedures on asymptomatic patients (without the classical symptoms suggesting cervical cancer to a clinician), the incidence is very close, namely 1·2 per cent for anaplasia and 1·3 per cent for non-invasive cancer over a period of 10 years. Where the incidence of cancer in one hospital practice bears no relation to these figures is seen in the 3·4 per cent of invasive cancer; this higher figure is due either to hospital selection, or to the patient's selection of that hospital. These writers also refer to regression of anaplasia (an incidence of 20–75 per cent) and conclude that anaplasia does not warrant immediate definitive therapy as for carcinoma, but it does call for close and continued ' diagnostic observation ', and this is the

second point in the relationship between the two lesions. They note too, as has already been mentioned here for non-invasive cancers, that many foci of anaplasia are so small that they could easily be removed by the Younge biopsy procedure.

The last point in the relationship of the two lesions is the thorny problem of the changes sometimes found in the cervical squamosa during (not necessarily caused by) pregnancy. The time of discovery is too often equated with causation, but there is no doubt there is a school believing that these changes are caused by pregnancy and therefore regress after the confinement; the other school believes the changes to be what they look like and, if full thickness changes, should be regarded as non-invasive cancer, pregnancy notwithstanding (Te Linde, 1956). There is, however, for both lesions, no immediate hurry for definitive treatment and with close diagnostic observation in either case the patient should not be in danger. It is probably fair to say that the present-day practice is to wait until six or nine months after a confinement before making a biopsy diagnosis. Certainly involution of the cervix may alter the contours from which a punch biopsy or a cervical smear is taken, leading consequently to different reports and confusion if there is no close cooperation between clinician, cytologist, and pathologist (Kaufmann and Ober, 1959). Further, as Carter (1956) has pointed out, we do not know the after-effects of diagnostic surgical procedures, including the effects on any remaining areas of non-invasive cancer. He felt that small residual areas might slough in the healing process, and lead to an erroneous conclusion in regard to ' reversibility ' of the lesion. This reasoning applies equally to the basal anaplastic lesion, and to the lesion of both types discovered during pregnancy. Similarly, repeated biopsy procedures on both types might conceivably lead to invasion.

In summary it may be concluded that there must be a close relationship between these two degrees of atypicality, and that, as the search for the major degree is bound to find minor degrees (one-third of McKay's cases of anaplasia had non-invasive cancer as well), then we must pay proper and prolonged attention to them, to serve the patient's best interests.

## THE PROBLEM OF DIAGNOSIS

Non-invasive squamous cancer cannot be seen by the naked eye, and as the epithelium is intact there are no symptoms, and no signs directly attributable to it. Diagnosis therefore is either accidental, from examination of cervices removed during total

hysterectomies and repair operations, or it follows enlightened biopsy procedures dictated by positive reports from cytology or colposcopy, carried out as screening procedures.

## Accidental Diagnosis

Prior to World War II, it was regarded as sufficient laboratory examination of any cervix accompanying a pathological specimen of uterus, to take one biopsy block from about a quarter of an inch of the diameter of the portio—more or less according to the size of the cervix. The same single block was made from cervices amputated during repair operations. These single blocks really only paid lip service to the acknowledged danger of cancer in this organ, as most gynaecologists of experience had been faced with an accidental finding of cancer at some stage of their careers and the shock left painful memories. But the lesion that was being excluded by this single block, was an early *invasive* lesion, and although the clinician felt he had missed something, he knew he could not see all the small invasive cancers, and the altruistic examination of one block was continued, and occasionally an invasive cancer was discovered. This custom and the expectation of an occasional discovery of an invasive cancer is all the more surprising when we consider the date of the first description of non-invasive cancer by Williams (1887) and the better known of Rubin (1910).

' Simple ' erosions were accepted as simple if the patient was in her twenties and with no intermenstrual or post-coital spotting, but regarded as clinically suspicious if the patient was in her late forties and did complain of these symptoms. It is only since World War II that this confusion about ' clinical suspicion ' has become clearer and that gynaecologists (Read, 1955) have been forced to acknowledge that they no longer know about the cervix simply by its appearance unless its appearance is of malignant ulceration or proliferation. The appearance of benignity is no longer trustworthy. It still has to be insisted that the term ' clinically suspicious ' should imply that a lesion has been seen (and biopsy of that lesion called for) rather than that the clinician, weighing up the patient's symptoms, age and parity *with* the appearance of the cervix, suspects that carcinoma might be responsible and arranges early biopsy; this is not a clinically suspect cervix, if words mean anything, but a suspect syndrome, to be equated with post-menopausal bleeding for example, where there may be no palpable or visible abnormality, yet early diagnostic curettage is accepted as essential to exclude fundal adenocarcinoma.

## Adequacy of Laboratory Specimen

With new work on the incidence of non-invasive lesions as accidental findings, with multiple biopsies—3·9 per cent (Auerbach and Pund, 1945) and Foote and Stewart's (1948) complete serial sectioning of cervices with non-invasive cancer, showing the bulk of these lesions to be at or about the junctional epithelium at the external os, it has slowly been realized that our single punch block made by the laboratory is hopelessly inadequate. Therefore to exclude invasive or non-invasive cancer, as an altruistic routine laboratory procedure, demands a sample of the junctional epithelium from its entire circumference, and taken at least ¼ in. above and below the actual external os, or any apparently simple erosion. This produces a ' ring ' of tissue which can be made into 10 or 12 blocks or more for histological examination and some real assurance may be given that malignant disease has been excluded. In other words, examination of an unsuspected cervix is now much more meticulous and comprehensive and only misses being perfect in that serial sectioning in each case is impracticable in most laboratories.

Should one or more of these blocks show that they did harbour an invisible invasive cancer, then the pathologist's report can confidently name it to be a Stage I lesion, and the clinician must reconsider full definitive treatment. But should a non-invasive cancer be demonstrated, the necessary steps, still short of serial sectioning, are somewhat different because the removal of the cervix and uterus is regarded as adequate treatment for this lesion *provided* we are satisfied we are dealing with no more advanced a neoplasm. To be satisfied of this calls for two further sets of blocks from the original specimen. First, from the endocervical canal above the first ' ring ' of tissue up to the internal os; this is best done by coring out the canal and making longitudinal or transverse blocks from it. Secondly, if there be a vaginal cuff *below* the removed cervix, blocks must be made from its entire circumference to exclude downward spread of the non-invasive growth. The discovery of further areas of non-invasive cancer above the original ring, but not as far as the internal os, with nothing found in the vaginal cuff allows a report to be given of probable complete removal of the lesion—though follow-up of these patients should be as thorough as for those with invasive cancer, since we accept that the lesion is cancer and has at least grave potentialities. Should the lesion extend to the internal os, then further blocks above this level must be made, until benign tissue is reached, or invasion discovered and reported. Should the lesion be discovered in the vaginal cuff edge, then further treatment is called

for as soon as feasible. It is now seen that this accidental diagnosis is largely a matter of the plan of examination of the cervix by the pathologist, along as realistic lines as he can afford time for, but the steps outlined must be regarded as minimal.

### Diagnosis where Suspicion of Cancer is only Raised by Positive Cytological or Colposcopy Examinations

Just as there may be varying degrees of malignancy, in type as well as extent of growth, so there are varying degrees of abnormality of the surface cells, and biopsy procedures may properly be initiated following cytology reports falling just short of positive. Many clinicians prefer a cytology report to be clear cut positive or negative, just as they may be impatient of a histological report which shows indecision and calls for careful observation rather than allowing of immediate treatment, or discharge, of the patient. The realization, from the study of these early cancers, that there is *no immediate hurry* to initiate biopsy, arises from the now accepted likelihood that the non-invasive cancers are latent for a very much longer time than invasive cancers. But some of the positive cytology tests are gleaned from early invasive lesions, and in spite of the successful guessing of some modern cytologists in forecasting whether a lesion be invasive or not from a study of its surface cells, this can never be more than educated guesswork and clinicians must remain concerned until a biopsy report is achieved. When we consider the variation in degree of atypical cell patterns, the full thickness of changes we accept as non-invasive cancer, the very early minute areas of true invasion now styled ' micro-carcinoma ', and the fully fledged invasive cancers, and remember that they may all be found in the one cervix, it is seen to be quite illogical to expect any sudden change in the surface cells just because the first few basal cells have at last broken away into the deeper connective tissue. No excuse is offered for repetition in this matter for it is only since the increased use of cytology as a screening method that so many non-invasive cancers have been found, and their proper diagnosis and management slowly realized. Papanicolaou's huge contribution to this study cannot be over praised as it has led to a new upsurge of the quest for cancer at a stage in its life where treatment is much more successful than ever before.

In Great Britain, the absorption of the significance of Papanicolaou's work with Traut and the ability to copy it had to wait until sometime after 1945, and even yet, obvious errors of management of this diagnosis occur from time to time, and clinicians continually have to be led from step to step slowly, to achieve a result in the