

SYMPOSIUM ON ABNORMAL UTERINE BLEEDING

Edited by
JOHN I. BREWER, M.D.



CLINICAL OBSTETRICS AND GYNECOLOGY

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SYMPOSIUM ON SPECIAL DIAGNOSTIC AIDS

Edited by C. PAUL HODGKINSON, M.D.

FOREWORD

The effort to be selective in this compilation of aids to accurate obstetric and gynecologic diagnosis has been deliberate. Because it would be unpropitious to include descriptions of every known test and procedure, only the newer tests of proved value have been included. These procedures are considered to be of value in the diagnosis of vague and poorly understood clinical conditions because that is where accuracy is most needed. Some tests may be considered controversial; others may be thought to be unnecessary because little practical value is apparent in their use, or because the ultimate form of treatment is unaltered. Yet, as a rule, the utilization of each procedure adds to the accuracy of diagnosis or leads to a better understanding of the basic nature of the illness.

The progress of medicine in particular and science in general has depended upon better means of recognizing and establishing basic facts. There has existed between the speculation of pure philosophy and the measured facts of pure science a zone of uncertainty—in time, current for all ages; in interest, stimulating and challenging to each curious scientist, and in character, by controversy. Always. the search has been for basic facts, the key to complete understanding. History glitters with the names of geniuses who have made some of these eminent discoveries.

No better example of the necessity of reducing a problem to its basic components before solving it can be cited than the simple geometric problem of determining the area of a circle. At one time this was the most challenging problem, and until pi was discovered, the area of a circle was approximated by the laborious process of the "method of exhaustion." Hippocrates, the mathematician (and not Hippocrates, the father of medicine), discovered pi. It appears probable that Hippocrates divided the circle into four equal parts forming arcs of 90 degrees, the radii being the angles. Hippocrates knew that by squaring the radius, the area of the square would be determined. He then discovered that the area included in the 90 degree arc within the area of the radius squared amounted to .7854; this multiplied by 4 was the area of a circle. Pi, therefore, amounts to 78.54% of the

figure 4, or 3.14159, the factor necessary for solving the geometry of circles.

World progress is measured by such giant steps, and medicine has progressed likewise. Gradually the frontier of philosophic controversy has been more and more reduced by the solid facts of scientific knowledge. The art of medicine in some respects has been replaced by scientific tests which are reasonably accurate, prodigious in number, and costly in price. However, the art and experience of practice are still the foremost aids of the obstetrician-gynecologist in diagnosis. No test replaces sound clinical judgment in estimating the ability of a patient to deliver her infant or the duration of pregnancy or labor, in accurately determining the extent of pelvic malignancy, or differentiating the true nature of a pelvic mass. Yet, the search for accuracy continues, and the various tests and procedures herein described reflect in part the efforts of the modern obstetrician-gynecologist to eliminate uncertainty in today's diagnostic procedures. Tomorrow there will be new tests, perhaps an 'obstetric-gynecologic pi.

The Editor wishes to express his gratitude to those whose contributions made this volume possible, particularly to Miss Mildred Majesse, his secretary; to Paul B. Hoeber, Inc., particularly to Mr. Paul B. Hoeber himself, who was most tolerant to a delinquent Editor; and to Mrs. Eunice Stevens, his able troubleshooter.

C. P. H.

DEVELOPMENTAL STAGES OF UTERINE CANCER AND THEIR DIAGNOSTIC APPRAISAL

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THE UNIQUE ACCESSIBILITY of the uterus to direct physical examination and to tissue and cell study has enabled gynecologists to study the early phases of uterine cancer and to define the role of incipient lesions that may prove crucial in the control of these diseases. Thus, we have learned that most of these tumors have a gradual, rather than explosive, onset and may indeed exist in a reversible form for some time, followed by a stage of surface or in-situ development which may be asymptomatic but can still be accurately detected by methods already available to us. These prodromal phases may cover a period of years.

This developmental concept of uterine cancer, both in the cervix and endometrium is surely one that will be applicable to malignant tumors in other parts of the body when the advancement of knowledge enables regional surgeons to sample their respective areas by cell smear and biopsy with increasing facility.

The direct channeling of bleeding from any uterine ulceration to the body surface, whether it be endometrial or cervical in origin, produces an early symptom very difficult for any patient or her physician to overlook, though frequently an endocrine interpretation is given to it on the unwarranted assumption that testing may be safely postponed.

Once we have come to understand our unique opportunity and responsibility in early detection of uterine cancer by recognition of its incipient phases, we will gain an assurance about the management of these tumors which will dissipate our own anxiety concerning these

diseases; it would appear that our patients will not only benefit from our increasing diagnostic and therapeutic armamentarium, but they will even gain confidence from the optimistic approach of their physician and will present themselves early and frequently for pelvic examination. They will quickly assimilate the knowledge that early uterine cancer is curable in almost every instance, that it can be discovered by uncomplicated diagnostic methods, and that surgical treatment is available which does not entail a prohibitive or even disagreeable recovery period.

It is not possible to successfully manage these incipient phases of uterine cancer clinically without a fundamental understanding of the histopathology.

CANCER OF THE CERVIX

Microscopic Evolution

It is probable that some cervical cancers have an explosive onset with prompt invasion, but these are probably a minority group. They have been called monophasic tumors in the European literature because of the absence of an intraepithelial phase; they may arise in the basal or

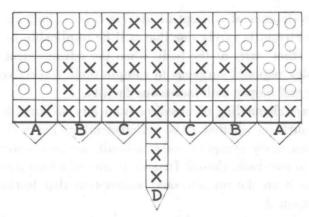


Fig. 1. Schematic representation of incipient phases of cervical cancer. A, normal squamous epithelium with usual active basal layer. B, basal-cell hyperplasia. C, intraepithelial cancer. D, early invasive cancer with basement membrane violated.

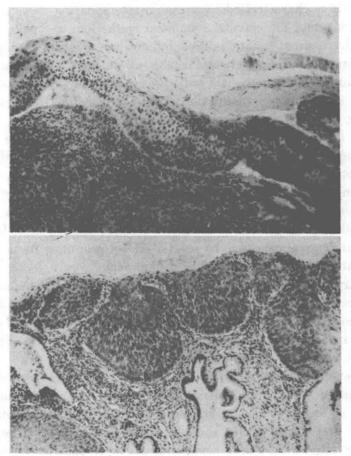


Fig. 2 (top). Basal-cell hyperplasia. Fig. 3 (bottom). Intraepithelial cancer.

parabasal layers of the squamous epithelium and promptly penetrate the basement membrane to invade the stroma freely.

We believe that most cervical cancers, however, have a much slower evolution with incipient, prodromal phases of considerable length, even years, marked by the histologic stages usually designated basalcell hyperplasia and intraepithelial cancer. Such a biphasic growth is probably the common sequential pattern.

Basal-Cell Hyperplasia. This asymptomatic, nonclinical lesion has been variously called cellular atypia, dysplasia, and cervical ana-

plasia. It is characterized by a malignant-appearing change in the deeper layer of the cervical squamous epithelium, the cells in this region having malignant qualities, but nowhere does this change rise to the surface to completely replace the full thickness of the squamous epithelium, for there appears to be preservation of some physiologic control which enforces maturation of these cells before they reach the surface. This maturation may sometimes be incomplete.

This abnormality of undetermined etiology appears to be in the true line of development of cervical cancer, for in some patients it has been observed to progress in this direction, and indeed, it is a commonplace finding surrounding intraepithelial cancer and even freely invasive cancer of the cervix. Probably this progression occurs in a rather small percentage of these lesions, and we consider this phase of cervical cancer to be reversible, because most frequently it disapears under observation without treatment.

It may be of interest to note that we found basal-cell hyperplasia to be present in the cervix of 1.8 per cent of 1000 women over 35 free of gynecologic symptoms or findings by routine cell smear and coning biopsy in our general diagnostic clinic. This survey also disclosed 16, or 1.6 per cent, intraepithelial cancers.

Intraepithelial Cancer. This designation is of course synonymous with cancer in situ of the cervix, preinvasive cancer, intramucosal cancer, or Stage 0 cancer. First described by Schottlander and Kermauner in 1912, it gained some attention in Germany through the histologic studies of Schiller and Robert Meyer and the colposcopic studies of Hinselman, but it was not thoroughly studied until the acceptance of the cytologic method of Papanicolaou fixed attention on early uterine cancer in this country. Numerous biopsy studies in the past 15 years have furnished histologic and clinical evidence to reinforce our belief that this lesion may be of primary importance in the solution of the serious problem of cervical cancer.

It has been alleged by some that the histologic criteria of this lesion are so poorly established that we cannot expect any uniformity of definition. I have not found this to be true amongst those who have actively studied this disease, though, of course, one must expect some irregularity in the understanding of all aspects of a relatively new

disease concept. The generally accepted histologic characteristics of this lesion include typical malignant-cell changes throughout all layers of the cervical epithelium with loss of stratification and polarity, hyperchromatic nuclei, increased nuclear-cytoplasmic ratio, and increased, sometimes atypical, mitotic figures. There may be variation in the size and shape of nuclei.

This malignant change is, of course, intramucosal and contained by the basement membrane throughout, but it may spread widely from its usual site of origin at the squamo-columnar junction or the histologic external os. It may be minute, small enough to be removed completely by a single biopsy, it may be in multiple foci, it may extend into glands, even replacing glandular epithelium completely, it may extend widely up the cervical canal and even into the endometrial cavity, or outward onto the portio and the vaginal epithelium. Of course, it must be intraepithelial throughout, for if the basement membrane is violated, it becomes an invasive cancer.

The intraepithelial phase of this cancer is probably irreversible for it will remain unless removed diagnostically or therapeutically. The evidence that this is a malignant lesion with a well-defined relationship to invasive cervical cancer falls into several categories:

- 1. The coexistence of intraepithelial cancer with frankly invasive tumors.
- 2. The frequent finding of tongues of microscopic invasion in lesions with a generally intramucosal pattern.
- 3. The median age of patients with intraepithelial cancer, 5 to 10 years younger than the median age of those with invasive cancer.
- 4. Increasingly frequent reports of intraepithelial cancer that have progressed without treatment to invasive cancer; such patients have been observed by all careful students of this disease. We do not know as yet the precise percentage of these patients that will develop invasive cancer without treatment; we do know, however, that it will be a significant figure, possibly 25 per cent. In such a case, it seems illogical to emphasize the percentage of those who do not develop invasive cancer, for it is evident that this condition may represent a major threat to such a patient's life or health unless she is subjected to a relentless program of observation. Certainly, in a patient whose

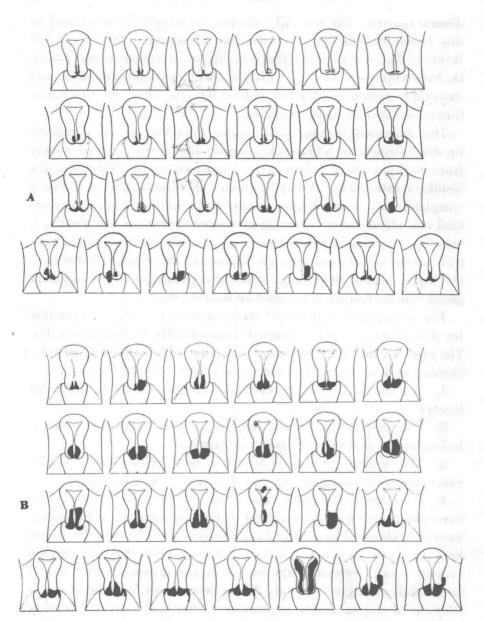
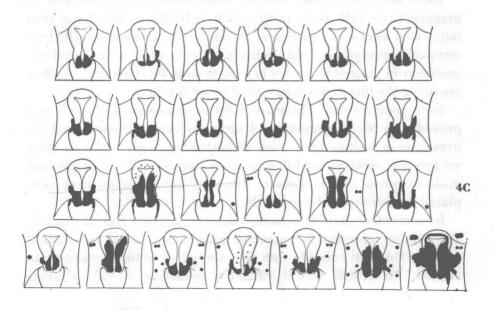


Fig. 4. Reconstructions of early invasive or freely invasive cancer of the cervix from radical hysterectomy specimens. Note initial invasion on canal side. A, early. B, moderately advanced. C (opposite), advanced.

uterus has fulfilled its childbearing function, surgical treatment would appear to be a conservative course of action.

Early Invasive Cancer. The histologic diagnosis of early true invasion of an intraepithelial carcinoma is a difficult and challenging problem. Pathologists are harassed by several considerations, such as the well-known stripping phenomenon of intraepithelial cancer, which diminishes its cohesiveness to the underlying stroma and, therefore, may make stromal interpretation difficult in spite of the utmost biopsy and laboratory care; the difficulty in distinguishing cervical glands plugged with intraepithelial carcinoma from islets of true invasion; and the frequent disappearance of the basement membrane beneath lesions that are undoubtedly intraepithelial, making the absence of this ephemeral structure a poor criterion upon which to hang the important diagnosis of invasion.

Of course, the clinician is faced with important therapeutic decisions, for the treatment of cancer in situ is strikingly different from that of invasive carcinoma. He finally comes to some sort of subclassification like intraepithelial carcinoma with areas of possible invasion, intraepithelial carcinoma with areas of probable invasion, intraepithelial carcinoma with tongues of invasion (an early but



definitely invasive tumor with a pattern of intraepithelial carcinoma remaining predominant), and finally, free invasion. This may enable him to sort out his therapeutic armamentarium into modest, moderate, and radical efforts consistent with the severity of the lesion. However, such attempts at classification are feeble, and we are badly in need of methods, either morphologic or perhaps cytochemical to establish definite invasion in cervical cancer. The patient's life may be sacrificed to an arbitrarily chosen treatment.

Pregnancy Changes. A change identical with basal-cell hyperplasia is common in the squamous epithelium of the cervix under the influence of pregnancy. It appears to be a reversible phenomenon, and most often it disappears after pregnancy. It is important to distinguish this pregnancy change from intraepithelial carcinoma, however, for the latter lesion may certainly be seen in pregnant patients, but it is not a pregnancy change, and it will persist after pregnancy unless removed by biopsy. This histologic distinction is important to make. We know it may be difficult, but it is extremely important to avoid classifying all incipient cervical cancers in pregnancy as pregnancy changes because the patient may be penalized for our ignorance.

There are several other cellular disturbances sometimes seen in pregnancy, as well as in nonpregnant individuals, that have been implicated as cancer precursors. Squamous metaplasia, so-called reserve-cell hyperplasia, and leukoplakia may offer some histologic problems in diagnosis, but we believe them to be irrelevant for they are not in the line of development of cervical cancer.

Geographic Spread. The gross evolution of a cervical cancer is best presented by the accompanying diagrams which represent actual patients whose lesions have been reconstructed from study of their microscopic sections, enabling us to observe the site of origin and mode of spread of this disease. These uterine diagrams have been placed in their order of magnitude.

It seems clear that the squamo-columnar junction and its immediate vicinity represent the common trigger zone for intraepithelial cancer. This will coincide with the external os in the absence of an erosion. An erosion, with its columnar epithelium, of course brings

this zone out on to the portio. This lesion tends to grow toward and up the canal more frequently than it grows out onto the portio. One also sees that early invasion tends to occur on the canal side most commonly, with frequently wide invasion of the stroma, before the portio is involved. In fact, one gains the impression that involvement of the portio is a mere geographic accident. The importance of the canal in the diagnostic management of this disease is obvious.

We must also note that spread to the parametria will usually precede nodal involvement. Embolization of cancer to nodes may be a factor, but extension through lymphatic channels seems to be a more important factor in spread.

DIAGNOSTIC MANAGEMENT

The History

All patients with basal-cell hyperplasia and the majority of those with intraepithelial carcinoma will be asymptomatic with respect to these lesions. Since these cellular disturbances do not cause ulceration, the patient usually does not exhibit abnormal uterine bleeding. In some, the lesion will create enough fragility in the epithelium to cause bleeding on contact so that the patient may note staining after douching, examination, or intercourse.

Of course, it has become axiomatic to teach our patients that the advent of menorrhagia, metrorrhagia, postmenopausal bleeding or change in the character of a vaginal discharge are reportable symptoms that require examination and appropriate diagnostic measures. No reassurance can be offered such a patient, however, without the completion of such diagnostic tests.

It is clear, of course, that pain is not a symptom of early cancer of the cervix; it is therefore of no importance in any regime of cancer control.

Pelvic Examination

Incipient cervical cancer gives no characteristic picture on examination. An intraepithelial carcinoma, even an early invasive carcinoma, may be present in a cervix that appears perfectly healthy and

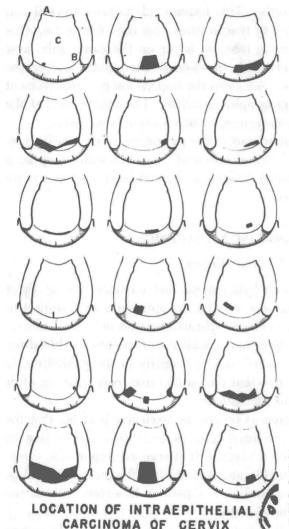


Fig. 5. Reconstructions of intraepithelial cancer of the cervix; C—cervical canal opened; B—squamous columnar junction; A—internal os.

epithelialized. On the other hand these lesions may be present in innocent looking erosions or conventional-looking beefy cervicitis. On occasion one may see cancer in situ represented by some minimal gross change like an exuberance or florid convexity in an erosion, or a whitish leukoplakic epithelium that might arouse suspicion upon careful examination.

There is no doubt that the careful, alert examiner with cancer