1953

Relationship of atypical endometrial hyperplasia to endometrial carcinoma

Alvin Charles Peterson
University of Nebraska Medical Center

THE RELATIONSHIP OF ATYPICAL ENDOMETRIAL HYPERPLASIA TO ENDOMETRIAL CARCINOMA

Alvin Charles Peterson

Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

February 27, 1953

Omaha, Nebraska

TABLE OF CONTENTS

The relation of endometrial hyperplasia to endometrial carcinoma has been a long discussed problem. In the past there has existed a great difference of opinion among gynecological pathologists on the relationship of these lesions. In the last seven years much has been done to bring these divergent views closer together.

A very possible explanation for the varied opinions can be explained, in part at least, by the criteria for diagnosis of endometrial hyperplasia and as to the type of hyperplasia.

It is the purpose of this paper to review the literature on the relationship of these lesions and the pathology of atypical hyperplasia. Two cases of endometrial adenocarcinoma that are known to have had previously diagnosed atypical hyperplasia will be reported.

The term hyperplasia is generally accepted as referring to the "Swiss Cheese" type of hyperplasia which Novak named in 1924. [1] "Swiss Cheese" hyperplasia is characterized by marked disparity of the glands, some are large and cystic, while perhaps others in the immediate vicinity are very small. In the last fifteen years there has been increasing interest in another type of hyperplasia in which the pattern

and staining qualities of the glands are altered. It is this atypical hyperplasia with which this paper is primarily concerned.

Atypical hyperplasia was probably first described, in part, by Cullen[2] in 1900, when he mentioned a pale staining epithelium which he regarded as the first recognizable sign of carcinoma of the corpus.

In 1922 Meyer[3] emphasized that there are only small differences in degree which separate endometrial hyperplasia from carcinoma and there are a small number of cases that are practically transitional. It is atypical hyperplasia which causes the pathologist the greatest concern as to whether the lesion is benign or malignant. From these statements and from his description of the lesion it can be assumed that Meyer in this report was referring to atypical hyperplasia.

Taylor[4] in 1932 divided endometrial hyperplasia into four groups. Three groups being various degrees of cystic hyperplasia and the fourth, a comparatively rare group, but of considerable importance in diagnosis and easy confusion with carcinoma. Of this fourth group he states that: "There are finally a few cases whose structure has many of the features of carcinoma. In these the glands are no longer truly cystic although they may exhibit marked variations in size, some being

small and round, others flattened, still others large and distorted. The epithelial band bordering the acini is greatly thickened, the nuclei lying at different levels in the cells so that the appearance is given of a multilayered epithelium. The nuclei themselves vary considerably but they are sometimes large with dark granules and a distinct nucleolus. A tendency to the formation of intraglandular projections is present in certain cases and in others there are occasionally suspicious areas of atypically staining epithelium.

Further, such descriptions of atypical hyperplasia were given by Novak and Yui[5] in 1936, Gusberg in 1947[6] and Novak and Rutledge[7] in 1948.

Hertig and Sommers[8] in 1949 list three lesions which have been described as atypical hyperplasia by other authors. They are: (1) Adenomatous hyperplasia, which is the outpouching of budlike, glandular projections into the supporting endometrial stroma. They eventually form small, closely packed glands, some of which lie back to back. (2) Anaplasia, which is shown by glandular lining cells that vary abnormally in size, shape, cytoplasmic staining and polarity. Their nuclei are of irregular shape, size and staining qualities. (3) Carcinoma in Situ, which is based

upon the presence of endometrial glands composed of large eosinophilic cells with abundant cytoplasm. The nuclei tend to be pale with small chromatin granules and slightly irregular nuclear membranes. The region of carcinoma in situ is usually focal and contrasts sharply in morphology and staining with neighboring unaffected glands.

In an recent article Speert[9] characterized the pathology of atypical hyperplasia as being "abnormal proliferative activity of the glandular epithelium, with one or a combination of the following attributes: (1) epithelial budding (2) tuft formations within the gland lumina (3) outpouchings of the gland walls (4) crowding of the glands (5) stratification of the epithelium and (6) pallor of the stained cells."

Reports of coexisting endometrial hyperplasia and endometrial carcinoma, or cases of hyperplasia known to have preceded carcinoma have appeared in the literature several times. However until reports of Hertig and Sommers[8] in 1948 and Speert[9,10] in 1948 and 1952 the actual number of cases were few and isolated. In most early studies it is difficult to determine the type of hyperplasia the author observed.

A review of these reported cases in chronological

order is evidence of increasing awareness of the relation of endometrial hyperplasia to carcinoma.

The first such case was probably that reported by Backer[11] in 1904 when he reported two cases of Corpus carcinoma developing in hyperplastic uteri. Meyer[3] in 1922 reported three cases of carcinoma coexisting with cystic hyperplasia.

In 1924 Horsley[12] gave a more detailed account of a case that was diagnosed by curettements as glandular hyperplasia. Eighteen months later curettements revealed isolated areas of frank endometrial carcinoma.

Ewing[13] in 1928 reported three cases of carcinoma arising in hypertrophic glands. Fluhmann and Stephenson[14] in 1928 investigated twenty-three cases of fundal carcinoma and found hyperplasia coexisting with the carcinoma in two cases. From the description given, however, the hyperplasia was of a cystic type. Bamforth[15] in 1931 also reported one isolated case of coexisting lesions.

Taylor in 1932[4] was among the first to call attention to hyperplasia of endometrium as a possible precursor of endometrial carcinoma. He reviewed histories of 122 cases of endometrial carcinoma. Of these there were two cases which he classified as almost

certainly having endometrial hyperplasia preceding the carcinoma. The description of curettements fits his group four of endometrial hyperplasia which was previously discussed. There were also four cases in which the characteristics of previous bleeding make it probable that a period of benign endometrial disease of unknown type preceded the carcinoma. The association of diffuse endometrial hyperplasia and carcinoma coexisting was found in five cases.

Novak and Yui[5] in 1936 reviewed 804 cases of endometrial hyperplasia and 104 cases of corporeal adenocarcinoma. In the hyperplasia cases they were chiefly concerned with cases with unusual proliferative activity, which produced pictures of varying degrees of approaching carcinoma. Of sixty-four cases of carcinoma, in which they were able to study sections of both cancerous and noncancerous tissue, 39.06% showed hyperplasia. Payne[16] in 1937 however only found an incidence of 2.4% hyperplasia with superimposed carcinoma.

Mazzola[17] in 1938 reported a case of endometrial hyperplasia in a girl 18 years of age. Curettements observed one and six years later again were diagnosed as endometrial hyperplasia. Fifteen years after the original biopsy a frank carcinoma developed.

Jones and Brewer[18] in 1941 studied sixty-eight cases of endometrial adenocarcinoma and found but two cases of hyperplasia coexisting. From their histological description these two were not examples of atypical hyperplasia.

In 1944 Morrin[19] reported four cases of endometrial carcinoma which had had previous biopsies that were diagnosed as endometrial hyperplasia.

Corscaden, Fertig and Gusberg[20] in 1946 review ed cases of 958 patients treated for benign uterine bleeding by radiotherapeutic menopause. These patients were followed for an average of 6.7 years each. Fifteen cases of endometrial carcinoma subsequently developed from this group. In six cases original curettements were examined and five showed atypical hyperplasia.

Speert[9] in 1948 reported three patients in one year who were treated for carcinoma of the endometrium who had had a curetage within the previous six years. Atypical hyperplasia was found in all three cases. One case five, one five and one half and one six years after the original curetage.

Speert and Peightal[21] in 1949 studied fourteen cases of adenocarcinoma of the endometrium subsequent to irradiation for benign pelvic conditions. Seven of the fourteen patients had had a curetage four to

nineteen years previously. Six of the seven at that time had atypical hyperplasia.

Hertig and Sommers[8] in 1949 analyzed 500 cases of endometrial carcinoma. Original curettements were available in sixty-seven cases. Of these thirty-five were rejected for various reasons, as insufficient material or doubt as to the primary site of carcinoma. This left thirty-two cases in which it was possible to study the endometrium from one to twenty-three years before invasive carcinoma was diagnosed. The authors, as previously described, list three groups of findings which have been classified as evidence of atypical hyperplasia: (1) adenomatous hyperplasia (2) anaplasia and (3) carcinoma in situ. Adenomatous hyperplasia was the most frequent endometrial abnormality found. It was found in nineteen of the thirty-two cases, adenomatous hyperplasia was found in every group from one to thirteen years before carcinoma and was most common one to five years before carcinoma. Anaplasia was found in thirteen of the thirty-two cases, most commonly one to five years before carcinoma. Six cases showed carcinoma in situ from one to eleven years before the diagnosis of invasive carcinoma. The greatest incidence of carcinoma in situ was found three to five years before invasive carcinoma.

In a study of the genesis of endometrial carcinoma in patients 19 to 35 years of age, Sommers, Hertig and Bengloff in 1949[22] studied sixteen cases in this age group. In previous biopsies five of the sixteen patients showed adolescent cystic hyperplasia and endometrial polyp formation. These changes were followed later by adenomatous hyperplasia and anaplasia. Carcinoma in situ was observed in four of the sixteen cases. In two cases the carcinoma in situ was found along with the invasive carcinoma and preceding invasive carcinoma in the other two.

Speert[9] in 1952 studied sixteen cases of endometrial carcinoma in which curetage had been performed prior to the diagnosis of carcinoma. In three cases carcinoma was present at the time of the original curetage but was misdiagnosed. In only two cases was curetage normal and in these cases curetage was nineteen and twenty-two years before carcinoma was discovered. Of the remaining eleven cases, all showed varying degrees of atypical hyperplasia between one and eighteen and one half years before the diagnosis of carcinoma.

CASE MATERIAL:

Records at three private hospitals, Immanual Deaconess Institute, Nebraska Methodist and Bishop Clarkson Memorial Hospitals, were reviewed for cases

of endometrial adenocarcinoma that had had curetage prior to the diagnosis of carcinoma. The histories were studied along with pathology records to determine previous diagnostic procedures.

Seven patients gave histories of curetage prior to the diagnosis of adenocarcinoma. Of these only three were available for study. Of the three available, two patients had atypical endometrial hyperplasia before carcinoma was present. Original curettements were taken eighteen months and eleven years before carcinoma was diagnosed. The third patient had chronic endometritis. Of the other four giving histories of previous biopsies two were from distant states and had been told that they had carcinoma of the cervix. One patient had a dilatation and curetage two years prior to treatment and was told that she needed radium treatment at that time but she was never told the nature of her disease. The seventh patient had two curettements three years previously and was told following the first that she had carcinoma, after the second curettment she was told that she did not have cancer. One other patient gave a history of post menopausal bleeding intermittently for ten years prior to curetage and diagnosis of adenocarcinoma.

Case #1.

Mrs. H. K., a 48 year old white female. The patient was first admitted to the hospital in August of 1946 for complaints other than gynecological. At that time she gave a history of irregular and more profuse menstrual periods for the past five or six years. Flow was heavy and lasted for seven days.

Her second admission was on Feburary 10, 1949. For one year after her first hospital discharge her periods continued to become more profuse and more frequent, as often as every two weeks. For the past two years her periods became much less frequent, having four or five periods a year. One month before her second admission she began spotting between periods for one to five days. A curetage was performed on this admission and atypical endometrial hyperplasia was present. (see figure 1)

The third admission was on September 25, 1950. She had had no menstrual periods or spotting since her last admission until three weeks before her third admission. At that time she had painless, constant, bloody vaginal discharge. This continued for one week. She then had irregular spotting for two weeks. A curetage was performed at this time and adenocarcinoma

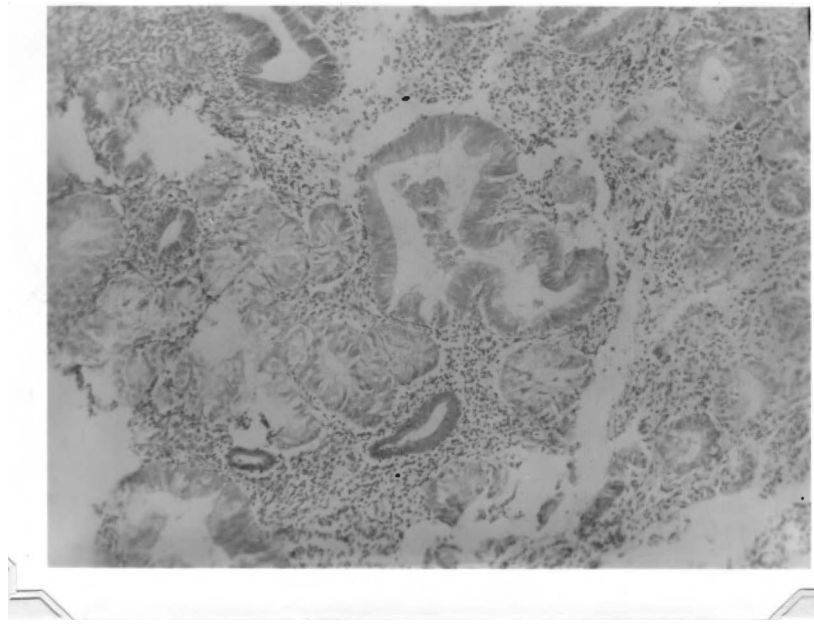

Figure 1. Case #1. Area of atypical endometrial hyperplasia in curettements. February 1949.

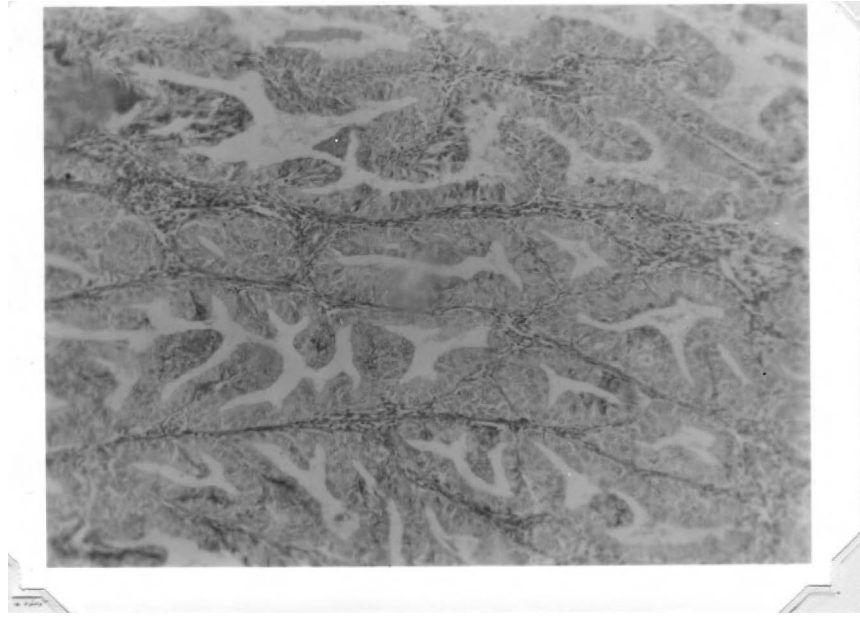

Figure 2. Case #1. Adenocarcinoma of endometrium from hysterectomy specimen. September 1950.

was present and a total hysterectomy was performed. (see figure 2)

Case #2.

Mrs. E. M., a 44 year old white female was admitted to the hospital for the first time on October 7, 1941. Her menstrual periods had always been very regular. Her July period, however, was normal in all respects except that it began a few days before it was expected. The same event occured in August. She had no menstrual flow during the month of September. In October at about the time of her regular period she had what her private physician described as massive uterine hemorrhage. A curetage was performed and atypical endometrial hyperplasia was present. (see figure 3)

The patient remained well until October 1952. She had had no bloody vaginal discharge or spotting since her first hospital admission. In October 1952 she began spotting every day or two. She was admitted to the hospital for the second time on November 12, 1952. A curetage was performed at this time and a diagnosis of poorly differentiated adenocarcinoma of the endometrium was made. A total hysterectomy was performed. (see figure 4)

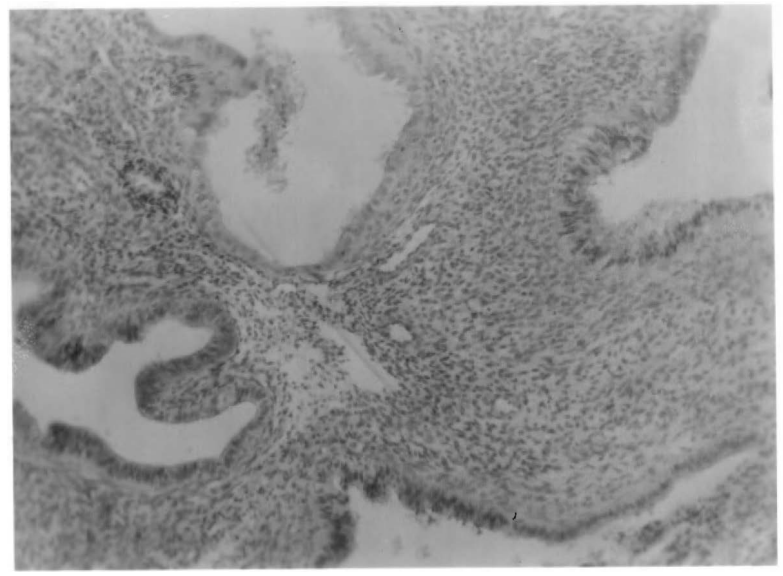

Figure 3. Case #2. Area of atypical endometrial hyperplasia in curettements. October 1941.

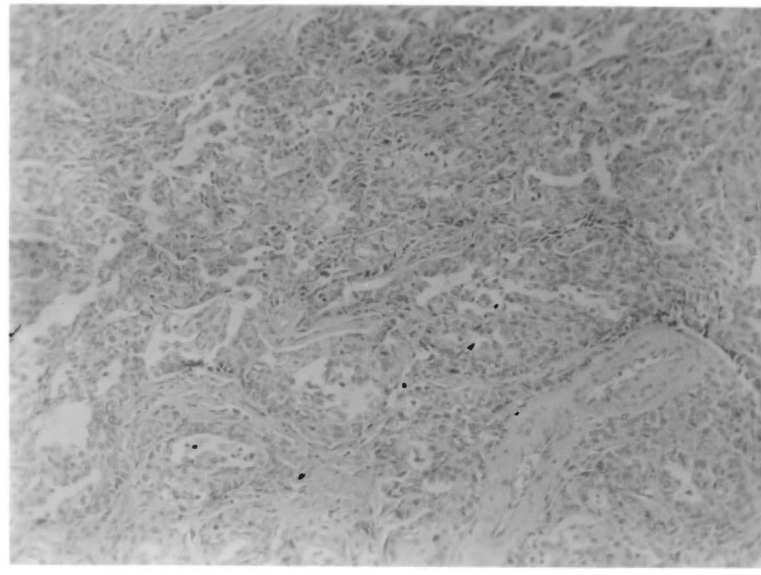

Figure 4. Case #2. Adenocarcinoma of endometrium from hysterectomy specimen. October 1952.

DISCUSSION

Despite the growing list of studies on the relationship of endometrial hyperplasia and endometrial adenocarcinoma the developmental stages of endometrial carcinoma are still somewhat controversial. Since the work of Taylor in 1932 there has been increasing interest in atypical hyperplasia. With the recognition and understanding of this diagnosis great strides have been made in conciliation of divergent views.

Speert[9] in discussing atypical hyperplasia states that "both the morphological pattern and the staining qualities of the glands are altered. These variants of the normal mucosa have been designated "atypical hyperplasia," "adenomatous hyperplasia", "carcinoid hyperplasia" and "carcinoma in situ of the endometrium." The last two terms possess new implications for hyperplasia of the endometrium, suggesting a relation to neoplasia, The borderline between hyperplasia and neoplasia is often difficult or impossible to delineate. Endometrial hyperplasia must therefore be classified into two distinct categories, functional and neoplastic. The first type is a clearly benign abberation, self-limited or easily reversible, associated with persistent estrogenic stimulation but probably without direct

significance for carcinogenesis. The second is less uniform in character and distribution, the glands may be disorderly, occasionally even presenting histological similarities to well differentiated adenocarcinoma. This type of hyperplasia thus possesses certain morphological attributes of neoplasia."

In a great majority of cases, endometrial hyperplasia is frankly benign. However, in a small minority of cases, it presents the features of atypical hyperplasia which cause the pathologists viewing the section a great deal of concern. As has been reported, one and the same section may show what is apparently a transition from a very benign type of hyperplasia to areas classified as borderline and also areas of frank carcinoma.

It was on viewing a section of atypical hyperplasia in Novak's laboratory that Josef Hablan stated: "Nicht Karzinom, aber besser heraus."[7]

The appearance of endometrial carcinoma following prolonged estrogen administration has frequently been reported.[10,23,24,25] The development of atypical hyperplasia following prolonged administration of estrogens has also been reported by these authors. Clemmesen[26] has reported a case of atypical hyperplasia of the endometrium that was strongly suggestive of

carcinoma following administration of estrogen.

Gusberg[6] believes, that the hyperplasia seen as an end result of endogenous (functioning ovarian tumors) or exogenous (estrogen therapy) estrogen stimulation is identical to atypical hyperplasia. He also believes that the histologic pattern of malignant endometria developing in patients who have received prolonged estrogen administration bears considerable resemblance to atypical hyperplasia. In some areas it appears that the process is but an intensification of an atypical pattern of hyperplasia. Present on the same section can be typical cystic glandular hyperplasia, atypical hyperplasia and adenocarcinoma.

Kimbrough and Muckle[27] have found many of the changes that suggest malignancy following estrogen therapy are reversible after cessation of therapy.

In approximately 10% of granulosa and theca cell tumors of the ovary there develops carcinoma of the endometrium. In these cases atypical hyperplasia has also been reported as carcinoma.

Payne[16] found that endometrial hyperplasia occurs five times more frequently postmenopausal than premenopausal. This has been the basis for the suggestion that postmenopausal hyperplasia especially favors

the development of carcinoma. Payne points out however, that postmenopausal carcinoma appears three to four times as frequently as premenopausal regardless of the type of endometrium.

Corscaden and Gusberg[23] observed that women with a history of menopausal menorrhagia, which is commonly observed with endometrial hyperplasia, have at least three times the expected incidence of subsequent carcinoma of the endometrium.

The findings of Sommers, Hertig and Bengloff[22] in their study of cases occurring at nineteen to thirty-five years of age, found that the same lesions were present in previous curettements in the premenopausal group as in the postmenopausal group.

The earlier authors on the subject of the relationship of hyperplasia to endometrial carcinoma recognized little more than a casual relationship between the two lesions. Payne[16] felt that the significance of the association between hyperplasia and fundal carcinoma seemed to be more in the danger that the hyperplasia may obscure the malignant change than in the likelihood that it favored the development of carcinoma.

This is in direct contrast to Taylor[4], Speert[9], Hertig and Sommers[8] and Corscaden and Gusberg[23] who

feel that atypical hyperplasia is a common precursor of endometrial carcinoma.

Novak and Yui[5] conclude that atypical hyperplasia is not to be looked upon as a precancerous lesion as indicating a lesion which predisposes to carcinoma but that it is one which represents a transition from benign to cancerous disease.

Only a small percentage of women who have atypical hyperplasia are known to ultimately develop endometrial carcinoma. However, the large number of cases reported in the last three years in which it has been possible to study previous biopsies suggest that the figure is higher than was previously believed.

It seems quite probable that carcinoma of the endometrium is a slow growing process. As suggested by Novak and Yui[5] atypical hyperplasia of the endometrium could possible represent a transition from a benign to a cancerous disease. If this process is reversible or not is yet to be proven.

If the preceding assumptions are correct the percentage of patients with atypical hyperplasia that subsequently develop carcinoma is probably quite high. However, many patients who have atypical hyperplasia probably die of other causes before actual malignancy

of the endometrium develops. It is necessary to follow a large number of cases of atypical hyperplasia at least twenty years to determine the actual number that develop carcinoma.

In view of present knowledge of atypical hyperplasia radical treatment is not now justified. However, once the case is so diagnosed the patient must be followed very closely. Curettements must be adequate as the two lesions often coexist and a small site of carcinoma is easily missed.

SUMMARY:

The pathology of a type of endometrial hyperplasia which is often difficult to differentiate from endometrial adenocarcinoma is presented.

The growing interest of this lesion and its relationship to endometrial carcinoma has done much to conciliate divergent views. A review of the literature is presented as evidence of this interest.

Reports of a relationship between atypical hyperplasia and endometrial carcinoma were isolated until the last fifteen years. With the recognition of atypical hyperplasia several authors have reported relatively large studies of the lesion often appearing together with endometrial adenocarcinoma and of atypical hyperplasia often preceding carcinoma from one to several years.

The possible role of excessive estrogen stimulation, either exogenous or endogenous, as an etiologic agent of both lesions is discussed.

Two cases in which atypical hyperplasia was known to exist nineteen months and eleven years before adenocarcinoma was diagnosed are presented.

That atypical hyperplasia actually predisposes to carcinoma cannot be stated definitely at this time. That there is more than a casual relationship between the two lesions however seems quite probable.

Carcinoma of the endometrium is most likely a slowly developing disease and it is necessary to follow a large number of cases of atypical hyperplasia for several years to accurately determine how many such cases subsequently develop endometrial carcinoma.

CONCLUSIONS:

In view of the two cases presented along with the growing list of similar cases the diagnosis of adenocarcinoma of the endometrium should be reevaluated. That there is more than a casual relationship between endometrial atypical hyperplasia and endometrial carcinoma seems most probable. Endometrial carcinoma is a slow growing lesion and a patient with atypical hyperplasia of the endometrium must

be followed closely for a period of several years. When endometrial carcinoma is suspected curettements must be adequate and studied in detail as the two lesions often coexist and a small area of frank carcinoma can be easily missed.

BIBLIOGRAPHY

1. Novak, Emil: Gynecological and Obstetrical Pathology. Philadelphia. W. B. Saunders Co. 2nd Edition: 163, 1947.

2. Cullen, T. S.: Cancer of the Uterus; its Pathology, Symptomatology, Diagnosis and Treatment; also the Pathology of Diseases of the Endometrium. New York. D. Appleton & Co. 1900. Cited by Speert, Harold: 1952, (9).

3. Meyer, Robert: "Plattenepithelknotchen" in hyperplastischen Drusen der Korpusschleimhaut des Uterus und bei Carcinom. Arch. F. Gynak, 115: 394-407, 1922. Cited by Taylor, H. C.: 1932, (4).

4. Taylor, H. C.: Endometrial Hyperplasia and Carcinoma of the Body of the Uterus. Am. J. Obst. & Gynec. 23: 309-332, 1932.

5. Novak, Emil and Yui, Enmei: Relation of Endometrial Hyperplasia to Adenocarcinoma of the Uterus: Am. J. Obst. & Gynec. 32: 674-698, 1936.

6. Gusberg, S. B.: Precursors of Corpus Carcinoma Estrogens and Adenomatous Hyperplasia: Am. J. Obst. & Gynec. 54: 905-927, 1947.

7. Novak, Emil and Rutledge, Felix: Hyperplasia Simulating Adenocarcinoma: Am. J. Obst. & Gynec. 55: 46-63, 1948.

8. Hertig, A. T. and Sommers, S. C.: Genesis of Endometrial Carcinoma. I. Study of Prior Biopsies. Cancer 2: 946-956, 1949.

9. Speert, Harold: Premalignant Phase of Endometrial Carcinoma. Cancer 5: 927-944, 1952.

10. Speert, Harold: Corpus Cancer; Clinical, Pathological and Etiological Aspects. Cancer 1: 584-603, 1948.

11. Backer, J.: Zwei Falle von Carcinoma Corporis Uteri. Zentralbl. F. Gynak. 28: 735-736, 1904. Cited by Speert, Harold: 1948, (10).

12. Horsley, J. S., Jr.: Report of a Case of Adenocarcinoma ofthe Body of the Uterus. Am. J. Obst. & Gynec. 7: 106-108, 1924.

13. Ewing, James: Neoplastic Diseases. Philadelphia. W. B. Saunders Co. 3rd Edition: 597, 1928. Cited by Taylor, H. C.: 1932, (4).

14. Fluhmann, C. F., and Stephenson, H. A.: The Coincidence of Hyperplasia Endometrii and Carcinoma Corporis Uteri. Surg., Gynec. & Obst. 48: 425-428, 1929.

15. Bamforth, J.: A case of Early Carcinomatous Change in Hyperplastic Endometrium. J. Obst. & Gynaec. Brit. Emp. 38: 614-617, 1931.

16. Payne, F. L.: The Clinical Significance of Endometrial Hyperplasia. Am. J. Obst. & Gynec. 34: 762-779, 1937.

17. Mazzola, V. P.: Endometrial Hyperplasia (puberty), Adenocarcinoma, Fifteen Years' Follow-Up. Am. J. Obst. & Gynec. 36: 698-701, 1938.

18. Jones, H. O. and Brewer, J. I.: A Study of the Ovaries and Endometriums of Patients with Fundal Carcinomas. Am. J. Obst. & Gynec. 42: 207-217, 1941.

19. Morrin, K. C.: Carcinoma of the Body of the Uterus. Surgical Clinics of North America. 24: 1179-1184, 1944.

20. Corscaden, J. A., Fertig, J. W., and Gusberg, S. B.: Carcinoma Subsequent to the Radiotherapeutic Menopause. Am. J. Obst. & Gynec. 51: 1-12, 1946.

21. Speert, Harold, and Peightal, T. C.: Malignant Tumors of the Uterine Fundus Subsequent to Irradiation for Benign Pelvic Conditions. Am. J. Obst. & Gynec. 57: 261-273, 1949.

22. Sommers, S. C., Hertig, A. T., and Bengloff, Harold: Genesis of Endometrial Carcinoma. II. Cases 19 to 35 Years Old. Cancer 2: 957-963, 1949.

23. Corscaden, J. A., and Gusberg, S. B.: The Background of Carcinoma of the Corpus. Am. J. of Obst. & Gynec. 53: 419-431, 1947.

24. Novak, Emil: Postmenopausal Bleeding as a Hazard of Diethylstilbesterol Therapy. J. A. M. A. 125: 98-99, 1944.

25. Fremont-Smith, M.; Meigs, J. V.; Graham, R. M., and Gilbert, H. H.: Cancer of Endometrium and Prolonged Estrogen Therapy. J. A. M. A. 131: 805-808, 1946.

26. Clemmesen, J.: Endometrial Changes Resembling Adenocarcinoma, Coinciding with Oestrin Treatment and Granulosacell Tumour of the Ovary. Acta Obst. et Gynec. Scandinav. 27: 384-389, 1948. Cited by Speert, Harold: (10).

27. Kimbrough, R. A., Jr., and Muckle, C. W.: Carcinoma of the Endometrium. Quart. Rev. of Obst. & Gynec. 9: 217-225, 1952.