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Endometrial carcinoma

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ENDOMETRIAL CARCINOMA

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INTRODUCTION

The history of endometrial carcinoma is still being written, as is the history of carcinoma and of medicine itself. There has been little formal history. In the history of gynecologic neoplasm, the one who seems to best convey the spirit is J. Marion Sims. The founder of gynecology was removed from the staff of the hospital he had created because of his insistence in treating cancer. The irony of this situation is heightened by the fact that it was female members of his hospital board who had him removed.(1) At that time it was feared as a fatal, contagious disease. Many today have the same idea and there is deep fear on the part of mankind toward cancer and great reluctance to admit its existence until it is too late.

The basic procedures back of modern therapy for endometrial carcinoma are of fairly recent origin. Freund accomplished hysterectomy in 1878 but its successful use in cancer treatment did not come until the turn of the century. Mortality following hysterectomy was at first very high. Wertheim, who employed hysterectomy in cervical carcinoma, had an immediate mortality of twelve per cent, while others were much higher.(2) Heyman, Lynch and others in 1920 showed the value of radium in endometrial carcinoma, but it is

only recently that improved surgery and improved radiation therapy have resulted in raising five year cures to the high levels reached by some clinics today.

INCIDENCE

There seems to be an increasing rate of incidence of endometrial carcinoma. Recent figures show a higher ratio of endometrial to cervical carcinoma. In New York State, exclusive of New York City, the rate is 11.9 per one hundred thousand as compared to 34.3 per one hundred thousand for cervical carcinoma. A factor to be considered is the somewhat disproportionate Jewish population in New York State. However, in Connecticut, where cancer is a reportable disease, 11.8 percent of all cancers are cervical, while 7.8 per cent are corpus cancers, or about 70 per cent of the cervical rate. Mayo Clinic figures give a ratio of 1:3, corpus to cervical cancers.(1)

Mortality: No separate mortality figures are published.* Use of the United States vital statistics (1943) gives a mortality of 12.7 per hundred thousand. This implies that, since the "gross" cure rate is almost exactly the same for both cervical and endometrial carcinomas, then about four thousand women

*The figures for 1944 show 17,152 United States mortalities from uterine carcinoma, but this is unreliable due to variations in reporting.(3)

die of endometrial carcinoma every year.(1)

ETIOLOGY

The etiology of neoplasms in general, must enter the background of this study. While the blastoma concept is long in the discard, it is well to remember that growth and embryonic development are nevertheless important factors. In the uterine mucosa, we have growth to the physiological extreme. The two chief factors which enter into the origin of neoplasm are, according to some, 1. growth, 2. involution. Again the uterus may be said to be an involuting tissue, par excellence. When one considers the ages of greatest incidence, 50-65, in wide studies, one is impressed with certain concomitant endocrinological facts; the gradual failure of progesterone production and the inversely proportional increase of estrogenic hormone, this due to the release of basophilic activity as the control by progesterone is lost. Since age exhausts the supply of follicles, this is to be predicted. Progesterone producing activity appears to be more a function of total follicle quantity rather than the one of greatest maturity only, as is sometimes diagrammatically represented.(3)(4) The positive correlation between nulliparity and corpus cancer,(TableI)

TABLE I

Pregnancy In Relation To
EndoMetrial Carcinoma
From Randall, Mirick and Wieben

Parity	No. of Cases	% of Cases	No. of 5yr. survivals.	% of 5 yr. survivals.
0	80	24.24	41	51.25
1	51	15.45	20	39.21
2	52	15.75	32	61.53
3	47	14.24	30	63.82
4	25	7.58	14	56.0
5	28	8.48	18	64.28
6	19	5.75	13	68.42
7,etc.	8	2.42	3	37.5
8	15	4.54	6	40.0
unknown	5	1.51	3	60.0
Total	330	99.99	180	54.5

Differences in percentage of Nulliparous Women in the Cervix and Corpus Series
from Corscaden and Gusberg.

	Total Nol	Per Cent	Diff.	+P.E.	% P.E.
Cervix	524	16.6	22.0	± 2.61	8.43
Corpus	192	38.6			

would seem relevant also, in that we have again a situation of continued high estrogen level as compared with progesterone. Defective and insufficient follicle formation may well be sufficient cause of the nulliparity and also of abnormal endometrium. Many studies with Warburg and other techniques and other techniques show altered oxidative enzyme systems in malignancies. It should be noted that this and other presumed peculiarities of neoplastic tissue have been called into question at various times and by various authors. Depression and alteration of tissue metabolism must exist for a period of time before it can become fixed. Which fact is also consistent with the occurrences in the endometrium. The great proliferation of glandular epithelium without sufficient rise in stromal elements causes compression, atrophy and necrosis. If the process be continued over a long enough period of time, tissue metabolism is altered, which alteration is considered by many to be a sine qua non of neoplasm formation. Though this explanation may account for certain developmental aspects, it does not explain loss of control of growth, but rather describes the background for later development of the neoplasm.(4)(5)(6)

Carcinogenesis: The problem of carcinogenesis of endo-

metrial carcinoma has not yet been solved. Some interesting theories have been propounded, however. One recent view, advanced by Hofbauer, is that oxidative enzyme systems are poisoned by arsenic which is found in larger concentrations in all rapidly reproducing cells. These cells are then further stimulated by the arsenic, which is a proven growth stimulant, a vicious cycle sets in.(7) In the discussion of endocrine and metabolic factors, it is important that the time factor be stressed. The unopposed estrogen stimulation, though of a minor degree, causes cystic glandular hyperplasia which fulfills the conditions for carcinogenesis in the same manner as more general hyperplasia.(4) There will be increased pressure, and increasing remoteness from the trophic supply under such conditions. The role of increased arsenic in such tissue may well be an important factor but cannot be evaluated at present.

Burrows points out some animal evidence in support of these concepts. Spontaneous uterine carcinoma occurs in rabbits which is closely paralleled by the presence of toxemia of pregnancy. Greene believes that these follow from the inability of the damaged liver to inactivate estrogen.

Gusberg reported that endometrial carcinoma often coexists with granulosa cell tumor of the ovary. This finding has been reported also from other clinics. Gusberg also reported adenomatous hyperplasia to be a precursor of endometrial carcinoma and found that corpus carcinoma occurred three and one-half times as often in women who had been irradiated for menopausal bleeding. This indicates that endometrial hyperplasia is associated with endometrial carcinoma in human females.(Table II)(9)

PATHOLOGY

Classification: Healy (1939) classified cancer of the corpus by size of the carcinomatous uterus. Group I includes uteri of normal dimensions. Group II uteri of size up to three months pregnant uterus. Group III all uteri larger than Group II. Crossen's classification (1937) is perhaps more valuable in prognosis and case analysis but in practice is almost too complicated for common use. He divides it into six stages on the basis of both macro and microscopic examination after removal of uteri.(10)

Stage I - Disease is confined to the endometrium.

Stage II - The myometrium is involved superficially.

Stage III - The myometrium is invaded to the serosa.

TABLE II

ENDOMETRIAL FINDINGS PRIOR
TO DIAGNOSIS OF CARCINOMA
from Hertig and Sommers
32 patients

Interval yrs.	Cases biop.	Neg. or no hyperplas.	Hyperplasia			Ana-plasia
			In-folding	Cystic	Adenon.	
15-23	6	7	2	0	0	0
10-13	8	0	0	6	4	2
6-9	13	2	2	7	6	4
3-5	10	3	1	4	7	5
1-2	3	0	1	0	2	2
Totals	40	12	6	17	19	13

Stage IV - The myometrium is as in III with ovarian metastases.

Stage V - There is involvement of neighboring organs; rectum, bladder, etc.

Stage VI - Local extension plus distant metastases.

Such classification affects therapy to the extent that wide extension into surrounding structures would render such tumors inoperable except palliatively.

Heyman (1929 and 1941) uses operability as the basis for his classification. Inoperable cases are such as have extended into parametrium, cervix, vagina, bladder, etc. and including distant metastases. Those considered operable are divided into two classes. The clinically operable are those cases where the tumor can be removed in toto and where operation is considered safe. Technically operable are those cases as above, but general health renders operation dangerous or inadvisable. This latter method of classification has come into considerable use in statistical studies. All "operable" cases can thus be kept separate from such cases as are far advanced from whatever reason. Finn, who made a thorough study of classification, Corscaden and many others think this is the most valuable classification clinically. Finn's own

classification was much similar to Crossen's except that stages V and VI were consolidated.

Macroscopic: Adenocarcinoma may begin as a widespread change in the endometrium, as multiple focii, or as a single isolated mass in the uterine cavity. The lesion may remain localized for months or years before invasion of the myometrium takes place. When invasion does occur, the stroma of the endometrium is first invaded, then later, as the disease progresses, there is penetration to the muscularis. Thence the disease spreads either outward to the parametrial structures, or alternatively, spread may be via the surface of the endometrium to the lower uterine segment, the cervix, and vagina.(12)

Common metastases are to the ovary, fallopian tube, mesosalpinx, and later to liver and lungs via the blood stream. This occurs in one-quarter of fatal cases.(13) The lumbar lymph nodes tend to be involved late and the tumor is likely to remain more or less localized for months. The inguinal nodes are seldom involved early and the obturator and hypogastric rarely. Of course, extension into the cervix creates a new situation in this respect. In the latter case, the obturator and hypogastric nodes are apt to be soon

involved.

Microscopic: A majority of these tumors are microscopically found to be well-differentiated columnar celled adenocarcinomas. There is often a complicated tubular or papillary formation of the proliferating cells. Also seen are areas of solid epithelial masses. Depending on the stage, diffuse areas of anaplasticity may be seen. Differing from these are adeno-acanthomas where areas in an adeno-carcinoma have taken on the characteristics of squamous epithelium. The stimulus which causes the cylindrical cells to revert to the basic coelomic epithelium is unknown.(14) Some carcinomata are so diffusely anaplastic that the term "carcinoma simplex" may be descriptive. Some of these may closely simulate sarcoma and render exact diagnosis difficult or impossible. Corscaden refers to the following histological types: papillary adenoma malignum, adenoma malignum, adeno-carcinoma, anaplastic carcinoma, adeno-acanthoma, and epidermoid carcinoma. At present, according to some authors, carcinoma-in-situ has no special status, but is simply considered non-invasive adeno-carcinoma. Radiologically, these tumors obey the general rule that the most differentiated are the

least radio-sensitive, while the least differentiated are the most radio-sensitive.

Carcinoma-in-situ:The recognizance of noninvasive endometrial carcinoma goes back fifty years. Cullen described and illustrated such cases in 1900. In the intervening period much disputation has taken place regarding precancerous lesions. Many have refused to admit the malignancy, in any sense, of a tumor not invading the myometrium. The work of Hertig and Sommers (16) is very convincing as to the reality of this entity. Their series consists of 32 cases of prior biopsies of endometrial carcinoma. Of these 6 showed definite carcinoma-in-situ, 2 were borderline, and 13 showed anaplasia. These total 21 of the 32 cases. Hyperplasia was even more nearly universal with only five cases negative. Of these five, two showed squamous metaplasia. Endometrial polyps occurred in ten cases of the series. Three of these showed suspicious epithelial activity. These were found from 6 to 13 years before the diagnosis of invasive carcinoma was made, and apparently undergo malignant change very slowly.(17) Adenomatous hyperplasia is the reverse of polyp formation. The growth potential is directed inward toward the stroma.

Budlike formation results, with groups of small, closely packed glands. Adenomatous anaplasia often occurs which then is equivalent to the alternative term "adenoma malignum" The next group in order of malignant potential is carcinom-in-situ. The criteria are; endometrial glands composed of large eosinophilic cells, pale nuclei, chromatin granules small, nuclei membranes irregular, and cytoplasm abundant. The cells are anaplastic, but in a concentrated focus with sharp contrast to surrounding glands in staining and morphology.

The principle back of calling these carcinoma is their irreversibility. Hertig and Sommers point out that such endometrium does not revert to normal, hyperplastic, or senescent endometrium. Unless destroyed, it is followed by invasive carcinoma. In a further study of eleven cases of carcinoma-in-situ which proceded on to invasive carcinoma, it was found that four of the eleven had carcinoma-in-situ and invasive carcinoma coexisting in the same uterus.(17) Granting the difficulty of recognition of carcinoma-in-situ notwithstanding, it is apparent that when it has been recognized, it has proceeded to invasive carcinoma. A questionable lesion with accompanying

hyperplasia and glandular anaplasia might also provide sufficient indication for surgery, or at least, close watching. Novais also expresses this view, and points out the danger in neglect of this situation.(3)(18)

SYMPTOMS

Bleeding is the most prominent of all symptoms. Post-menopausal bleeding is the most obvious danger signal and calls for immediate investigation. Bleeding is not universal, however. The patient may notice only a watery or leukorrheal discharge, Since many conditions may cause such discharge, change in the character or consistency should be regarded with profound suspicion. A brown or red color, a foul odor, a marked increase; all represent significant change. Symptoms should be regarded in light of the time factor. Intermenstrual and post menopausal bleeding or discharge should be investigated. Bleeding may be irregular at first, if only a few friable tags are involved. Later, bleeding may become continuous. Pain is not a prominent symptom but is often of the cramping type due to expulsive efforts on the part of the uterus. Extension to other structures will result in pain in later stages due to pressure, occlusion and

other causes. In such case, it is a symptom of the extensions rather than the disease and of limited value.(3)(19)(20)

If early carcinomas are to be detected, then it would seem that attention should be directed to the comparatively minor complaints found early in the course of the disease and some sort of screening applied. The latter will be discussed later. Abnormal bleeding and leukorrhea are, as previously mentioned, the earliest common complaint. For example: in Randall's series, the former accounted for 92.7 per cent, the latter 5.1 per cent, or a total of 97.8 per cent of all complaints.(21) Public education to get the patients in earlier, and through physician follow up might profitably be based on emphasis of these two factors. A factor to be considered is that delayed menopause, in and of itself, may be considered a symptom. In Randall's series, 56.7 per cent were women who had menstruated beyond the age of 50. Corscaden and C.L. Randall have similar statistics and draw similar conclusions. Associated disorders which seem significant are in J.H. Randall's series, Most common is cardiovascular disease with 44.2 per cent of all cases. Other significant findings are as given in the accompanying table.(Table III)

TABLE III

Diseases Associated With Endometrial Carcinoma

Taken from 225 cases where complete background information was available in J.H. Randall's series.

None	78
Fibroids	81
Polyp, Cervical	30
Benign ovarian tumors	9
Malignant ovarian tumors	77
Feminizing ovarian tumors	5
Pelvic inflammatory disease	36
Endometriosis	33
Other misc.	15

Survival Rate of Endometrial Carcinoma in Relation to Associated Diseases in J.H. Randall's Series

Associated Disease	No. Cases	% Cases	No. 5yr. Sur.	% 5yr. Sur.
none	143	43.3	83	58.0
vascular disease	146	44.2	79	54.1
diabetes	22	6.6	10	45.4
Misc.	19	5.7	8	42.1
	330	99.8	180	54.5

Hertig and Sommers noted a frequent (44 per cent) occurence of obesity in a group of 389 cases. Normally 34 per cent occurence of obesity is expected in the same age group,and 1.3 to 6.9 per cent of women from the general population had diabetes in other studies. Diabetes Mellitus was present in 9 per cent of Hertig and Sommers' cases.(16) A high incidence of vascular disease was also found, 44.2 per cent, in the preceding table. All these factors taken together seem to give us the picture of a cancer prone group. These things can only be reckoned as suggestive of study at the present state of our knowledge. They also point to an underlying pathologic metabolic process. The theory of liver failure recurs in the literature. Failure of detoxifying hormonal principles might logically provide a common cause for obesity,hypertension, diabetes, and gonadal imbalance. There has been no significant proved abnormality of the liver, either physiologically with present tests, or in histopathological studies. The underlying pathology is yet unrevealed. (3)(4)(16)

DIAGNOSIS

The diagnosis depends primarily on microscopic

examination of suitable tissue. There are many indicative and presumptive signs, however. Any evidence of overactivity of the endometrium demands investigation, including younger age groups. The most important diagnostic means is dilatation and curettage. A good instrument is a small ring curet with finely serrated edges. The instrument should not be too large since the "feel" of the instrument may be lost if it is too bulky. The entire endometrial surface should be gone over, noting any areas of softening, irregularity, or undue resistance. The specimen should be immediately placed in preservative solution. It is of aid to the pathologist, however, if the specimen be cleaned of unnecessary clot. This may be accomplished by means of placing the tissues on a sponge first, and then removing to solution. The clot shows a tendency to adhere to the sponge and separation is facilitated. Frozen sections are not considered completely satisfactory. Good quality embedded sections enable better examination and more positive diagnosis. If negative, then it is even more important to be able to exclude with accuracy and thorough search is needed to discover localized carcinoma-in-situ. (19)(20)

An important consideration for the clinician is cognizance of the fact that finding one source of bleeding does not rule out other sources. Since endometrial hyperplasia is frequently associated, if not actually a precursor, a high index of suspicion must be maintained in the presence of this condition.(9) Benign erosions, cervical polyps, and myomas do not exclude, by their presence, the existence of corpus cancer. Since myomata undergo parallel involution to the uterine wall, any woman whose myomata continue to give trouble postmenopausally should be investigated also.

At curettage, the following gross findings are of value: The vagina in malignancies shows less atrophy, pallor, and thinning of the vaginal lining. A patulous type of cervix in an older woman suggests the presence of an intrauterine mass. Hyperplastic tissue is smooth and glistening on the surface and granular on the deep side. If the proportion of glandular elements be large the tissue will be friable and somewhat simulate carcinoma. If the tissue be carcinomatous, however, the fragments will be of irregular shape. The free and cut surfaces will be indistinguishable and no smooth, glistening surface

will show. A nodular appearance of the surface is also highly suggestive. Adenocarcinomatous tissue is typically inelastic and friable and tends to separate easily into soft granular masses when pressed. Such tissue is also usually soft and formerly was the basis of a widely used technique, the Clarke test. This consists of palpation of the uterine wall with a sound. Free bleeding was, in fact, considered pathognomonic by Curtis and Huffman. The sinking of the instrument into the wall with delicate pressure is also strongly positive evidence. The presence of necrotic polyps or myomata may lead to false conclusions. An inherent danger of any instrumentation is the dislodgement and spread of cancer cells via blood and lymph.(3)(13)(14)(23)

Roentgen examination may give some idea of the extent of the mass, and displacement or compression of structures. Examination of the rest of the body may be of much value in discovering metastases. Early in the course of the disease, however, roentgen techniques are of little value. The methods of curettage and biopsy remain the chief diagnostic aids in early discovery of both corpus and cervical carcinoma.

It is found that extension to the cervix is fairly common. Cervical biopsy therefore, seems in

order at the time of dilatation and curettage. Conversely, when the need for cervical biopsy arises, it seems in order that the endometrium should be investigated also.(14)

Cytology: Formerly this has not been done but as the Papanicalaou technique has been perfected, it may become more practicable. A cannula has been devised which has been used with considerable success. The endometrial smear technique has not been as accurate as cervical smears previously. A controlled study is now underway at New York University-Bellevue. (24) Preliminary phases of this study have been extremely promising. The smear is taken by inserting the cannula into the uterine cavity and gentle suction is exerted by means of an attached syringe. The aspirated material is then placed on slides and fixed. At the above center, the usual Papanicolaou staining technique is used, employing Harris' hematoxylin, OG6, and EA50. Papanicolaou and Traut earlier reported an accuracy of 86.6 per cent ie. the remaining percent are false negatives. (25) This seems accurate enough to warrant using the technique where currettage is not contemplated. Furthermore, much higher rates of accuracy are predicted from aspiration techniques, but

controlled studies must be awaited. There is no reason, of course, why both methods may not be used. In cervical carcinoma Graham, Sturgis and McGraw found that the combined method was inaccurate in 1.7 per cent of cases, which represented an increased accuracy of 7.1 per cent over biopsy alone in their hands.(26)

Cytologically endometrial carcinoma does not show the marked changes evident in carcinoma of the cervix. Cytologists classify them into two groups, differentiated and undifferentiated. This system is based on the presence or absence of cell borders. Though not as sharp in outline as the squamous counterpart, differentiated malignant endometrial cells have a definite border. The cytoplasm displays considerable vacuolization. This may result, if marked, in the nucleus being pushed to one side, giving a "signet-ring" appearance. Also characteristic are enlarged nuclei up to eight times the size of a leukocyte. These nuclei tend to be eccentric in position. Hyperchromatic and marked granularity of the chromatin network are further characteristics showed by malignant cells in general.

In contrast to the differentiated adenocarcinomatous cells, the undifferentiated cells tend to group

together with no distinct cell borders between them.(24) There is less vacuolization and the nuclei present the usual atypical mitotic figures, hyper chromatism. It is, difficult, practically, to obtain sufficient quantity of cells or to distinguish the origin of such cells. Aspiration smears ease this problem considerably.

TREATMENT

At present three main choices of treatment are open to the clinician. These are 1. surgery (hysterectomy), 2. radiation and 3. a combination of these. In some studies, surgery has the best survival rate. For example, Arneson achieved 85 per cent five year cures when surgery was used alone, compared to 68 per cent for the combined method.(27) McKelvey, for example, found a rise in the five year cure rate from 58 per cent to 68 per cent in a ten year period. (See Table IV) During this time the attempt was made to drop the combination method in favor of pan-hysterectomy alone. These series are probably deceptive in that the surgical cases are highly selective. The favorable cases wherin spread is purely local are apt to come to the surgeon. The radiologist is more apt to get those cases where spread to other

structures has taken place. Corscaden compiled an average from the literature in 1950 of 39 per cent five year cures with radium alone.(28) The radiumhemmet figures show a forty five per cent five year rate by radium.(29) Scheffey achieved fifty four and eight tenths with radium treatment only.(See Table 4) The combined method was formerly apt to be "throwing the book" at the cases considered hopeless. It is now routine in many clinics to irradiate prior to hysterectomy. In some cases, radiation is employed post-operatively. Preoperative radiation is reported as yielding significantly higher results with an average of about seventy per cent five year survival having been reported, with several authors reporting above 90 per cent.(14)(30)

Surgery at present is undergoing reevaluation. The suggestion has arisen from McKelvey, Corscaden, Schmitz, and others that a more radical type of surgery will be employed in the future. A radical Wertheim type operation or Latzko operation followed by extraperitoneal lymph node dissection seems to be the commonly suggested operation for the future. The iliac nodes are much more commonly affected than once supposed as has been shown by Randall and others. The

TABLE IV

Adenocarcinoma of the Endometrium (Reportable)(38)
By McKelvy (from the Uni. of Minn. Med. School)

Year	Total No.	Surgical Rate	Absolute 5 yr. cure	Type of Treatment Attempted
1928-38		35.05	43.5%	Large proportion treated with rad. and X-ray.
1939-40	38	66.0%	58.0%	Treat as many as possible with rad. & panhysterectomy.
1941-46	116	67.0%	57.8%	Try to drop X-ray treat as many as possible with rad. & panhysterectomy.
1947-49	37	86.5%	*68.0%	Try to drop X-ray and radium, treat as many as possible by panhysterectomy

*Calculated survival rate using 1939-46 experience of relation between two year survival rate and five year cure and applying it to 1947-1949 two year survival.

Report of L.C.Scheffey

Treatment	Patients	Survival	Percentage
Adequate Surgery only	16	10	62.5
Adequate or inadequate surgery, with or without irradiation(unplanned)	44	21	47.7
Radium only	31	17	54.8
X-ray only	2	0	0.0
Radium and X-ray	38	17	44.7
Preliminary radium plus adequate surgery (no post operative X-ray)(planned)	46	42	91.3
Follow up 100%, overall operability rate 60%.	177	107	60.4

percentage of such metastases has been found in about 25 per cent of cases which were treated by irradiation only. These were more difficult and advanced cases but it makes obvious the existance of the problem. When the lesion actually reaches the cervix, as many parametrial, paracervical, and iliac group metastases are to be found in endometrial carcinoma as in cervical carcinoma.(6)(21)(31)(32)

While hysterectomy and radiation have been widely used, no studies could be found evaluating radical surgery and radiation used together. Corscaden believes that the inguinal nodes should be dissected as well as iliacs. He emphasizes that at present, however, proper treatment consists primarily of preoperative radiation and surgery. This latter to consist of at least total hysterectomy with bilateral salpingo-oopherectomy. He feels a Wertheim procedure with dissection of iliac and inguinal nodes to be valuable if the skill of the operator be sufficient.(33)

Radiation Therapy: Although much recent progress has been made with external roentgen therapy, the best results have been recorded in the literature with intracavitary radium. Extremely high voltage X-ray machines of order of 2000 K.V., and new techniques of

directing rays toward the carcinoma may result in more favorable statistics for this method. There are situations in which X-ray radiation is indicated. Where extension has proceded to the rectum and widely through the pelvis, external radiation may become the procedure of choice. Schmitz advocated routine use of external radiation as adjunct therapy where both preoperative radiation and hysterectomy were also used. Others advocate this procedure also but further survival reports are few. When employed nowadays, the standard technique is the employment of 200 K.V. multiple ports and a small daily dosage carried out for a long period of time.(30)

Radium therapy has been used in a variety of ways. The emitted dose has varied from 1200-9000 milligram hours in the past. The dose has been delivered in most cases by means of a tandem distribution of radium sources. The tandem has been employed for years, although severely criticized by Lampson in 1920, and the development of the packing technique as demonstrated by Heyman.(34) It is probably effective in most cases due to the shrinking of the uterus during treatment. Packing the uterus with capsules is a widely accepted method today. The capsules each have

attached a flexible wire cable and numbered tag. The capsules are inserted with a special introducer. The order of placement is noted so that they may be withdrawn in reverse order. The number of capsules varies with the size of the uterus to be packed. Containers may vary in size but still hold the same amount of radium, often 10 mg. Doses vary with the size of the installation. With 50 mg., 5000 to 6000 mg. hours is delivered, depending on the thickness of the uterine wall. If 100 mg. were used, the dose should be reduced to 4000 mg. hours, lest the greater intensity cause damage to the hollow viscera. The effect of radiation on these is the determining factor in dosage. If the dosage be delivered fractionally, certain benefits accrue: there are more cells treated in the effective stages of mitotic division and by shrinking of the uterus, greater area is brought nearer to the source of radiation. McGoogan and Hunt point out the relatively greater recovery of normal cells in comparison with cancer cells in the radiation free intervals. They used 65 mg. for 30 to 36 hours and spaced treatment 12 days apart.(35)

The dangers in the use of intracavitary radium are; injuries to bladder and rectum and perforation

of the uterine wall. The former is less likely than in cervical radiation and may be avoided by carefully calculating the dosage. The latter can be avoided only if great caution is used. All authors agree that the skill of the operator is taxed at times to discern the position of a boggy uterus and avoid perforation of a softened, necrotic wall. Experience and a cultivated sense of touch are invaluable here. If an accident should occur, the intracavitary radium should be discontinued. In operable cases, immediate surgery may be employed. External roentgen therapy may be resorted to with a good chance of favorable results. In addition to being a substitute for radium, the uterus may shrink and harden so that radium may again be used later.(30)

The advantages of one type of radium delivery over another is widely discussed in recent literature. The use of any method which delivers an adequate dose to the endometrium should be satisfactory. Two proposed methods seem to be preeminent, however. Both are based on sound principles and yielded good results on trial. One is the method of Heyman which is essentially the packing technique described.(34)(36) The other is the Y shaped hysterostat advocated by Schmitz.

The packing technique gives a more even dosage and is, perhaps, a little better suited to delicate adjustment in the presence of weakened uterine walls. Schmitz finds that radiation, 4000 r of 800 K.V. X-ray shrinks the uterus and that the Y hysterostat may then be fitted with ease and safety. This device consists of a 50 mg. radium capsule in each of the three arms of the Y with 6000mg. hours being the standard dose. Further, he finds that in ordinary cases there is considerable shrinkage after radiation. Thus on subsequent doses the arms of the capsule come to lie in direct contact with the walls of the uterus. Schmitz has carefully studied the dose delivered from the Y capsule and finds an adequate dosage delivered of the order of 100 per cent.effective, as far as the endometrium is concerned.(See illustration) Since no means yet devised can reach the serosa and deeper myometrium, this must be counted as adequate. Schmitz has attempted to to prove the effectiveness by studies of pathology. Paraffin sections showed radionecrotic plaques in all cases and in some cases complete necrosis of the endometrium. Though this might seem to argue the feasibility of complete cure by radiation alone, Schmitz and others are firm in their advocacy of

surgery in operable cases. The constant finding of necrotic plaques demonstrated a radiation dosage of 20000 to 50,000 gamma roentgens to the endometrium. This is confirmed by Nolan who found tissue necrosis and tumor growth inhibition in this range.(37)

It is perhaps in order to discuss the rationale of pre-operative radiation. Novak states the following as advantages: The cancer cells are devitalized. The cells are imprisoned by the fibrotic reaction produced by radium or roentgen radiation. The lesion is sterilized which reduces operative hazard. The greatest disadvantage is the delay period between radiation and operation, generally about six to eight weeks.(3)

Education: Of considerable importance in considering therapy, is the education of the public. The setting up of screening organizations or clinics should be of great value in reducing morbidity and mortality due to endometrial carcinoma. This tumor is peculiarly isolated in its early stages and tends to break its confines late and en masse. Cytology and aspiration biopsy seem to be the best available techniques for gynecologic screening clinics. While "tumor clinics" have not been sucessful in smaller urban areas, it

would seem to rest as a responsibility of the general practicioner as well as the gynecologist to further this work. Certainly, in any case, the practitioner should biopsy any case rendered suspect by the diagnostic criteria previously given. The index of suspicion must be high, or many will be missed early when a cure is likely.(1)

SUMMARY

The problem of endometrial carcinoma is considered. The magnitude of the problem is brought out by the mortality figures for uterine carcinoma, 17,152(1944), one-third of which represent endometrial carcinoma. The etiology is discussed primarily from the standpoint of endocrinology. Excess estrogen stimulation of the uterine mucosa is postulated as the point of departure for the carcinogenic process. The theory is outlined that this arises due to diminution of total number of follicles with age and other factors, and consequent loss of protective power of progesterone. Lost are both a supressor of anterior pituitary secretion and a factor in the cyclic changes which cause the periodic shedding of decidua. Anterior pituitary activity is an importan factor. There is an obscure relationship between diabetogenic and gonadotrophic activity is shown by statistics. Obesity and diabetes are frequently associated with endometrial carcinoma. The detoxifying role of the liver while an obvious factor, remains completely unevaluated. It is assumed because of the common finding of uterine hyperplasia that the level of equilibrium is higher in in these patients and/or operative over a longer period

of time than in normal patients. Estrogen administration is seen as a contributing factor both by virtue of direct stimulation of uterine mucosa and by the increased anterior pituitary stimulation after withdrawal of the suppressant action of the estrogen. There is a marked increase in anterior pituitary activity for a period of time thereafter.

The classification of Endometrial Carcinoma is discussed with division into operable and inoperable being accepted as clinically valuable. The system of Crossen based on spread is presented as more accurate. In this system, Atage I represents the stage of confinement to the endometrium. Up to Stage III, the uterus alone is still involved. Stages IV, V and VI representing spread to ovaries, neighboring structures and finally distant spread.

The pathology of these lesions is considered with possibility of multiple foci in the beginning. The lesion is seen as slow growing, and early confined within the myometrium. Common sites of metastasis are seen to be local; early to ovary, tubes; and vagina with distant metastasis occuring late. The micropathological picture of well-differentiated, columnar-celled adenocarcinoma is usually seen. Increased ana-

plasticity may be seen to the point of searcoma like appearance, but it is not common. The problem of carcinoma-in-situ is discussed with evidence from recent literature that this is part of the natural history of carcinoma. Emphais is made that these are irreversible lesions and therefore are malignant and call for surgery.

In discussing symptoms, the subtle and non-characteristic nature is emphasized. Minor bleeding which may seem to be only prologation of the menopause,watery discharge, excessive flow, may all herald this disease. Danger signals are the presence of obesity, diabetes, and hypertension, all of which show marked increase in incidence in association with endometrial carcinoma. The increaseing value of cytologic screening tests is discussed. In suchtests, the use of a special cannula has improved the Papanicolaou technique. Criteria are cytoplasmic vacuolization, eccentric nuclei, with hyperchromicity and granularity of the chromatin network, are dommonly employed. It is emphasized, however, that diagnosis is proved only by dilatation and curettage. The grossly griable tissue is quite characteristic, being the basis for Clarke's test, but presents the danger of perforation.

The three main choices of treatment are considered as being surgery, radiation, and combination of pre-operative radiation and hysterectomy. In spite of selectivity of surgical cases, it is seen that radiation alone has yielded nearly as good results in some clinics. It is evident from various current compilations that the statistical advantage rests with combined treatment. The best surgical report is 85 per cent 5 year survival in selected cases while radiation-hysterectomy has produced above 90 per cent in several clinics. The radiation is currently given in dosages of the order of 4000 to 6000 mg. hr. with intervals of ten to fourteen days between treatments. Of great importance is the method of delivery. Either the packing technique of Heyman, using tagged capsules usually containing 10 mg. of radium or the Y hysterostat of Schmitz are currently acceptable techniques. A dose of 20,000-50,000 gamma roentgens can be thus delivered as proved by necrotic plaques and such is an effective dose. In some cases, notably, in those with very friable uteri, X-ray is of no value. At present 200 K.V. in small, often daily, doses for several weeks, is the usual method. Multiple ports are used. The use of radical dissections, as radical Wertheim, is considered but no comparative figures are available as yet. Gynecological surgeons

are agreed that such procedures are very difficult, but probably of some value in the hands of skilled operators.

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CONCLUSION

Endometrial carcinoma is seen to be a slow-growing lesion with a precedent history of hyperplasia, anaplasia, and carcinoma-in-situ. These are predicated to be on a basis of endocrine imbalance due to an inherent, probably anterior pituitary factor, plus progesterone failure at the menopause. It is important that the public be educated to present themselves for screening when early non-specific signs appear. Aspiration and Papanicolaou smears are of screening value. Treatment is best carried out by a combination of preoperative radiation with radium capsules and total hysterectomy.

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