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Treatment of carcinoma of the cervix

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THE TREATMENT OF CARCINOMA
OF THE CERVIX

by

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THE TREATMENT OF CARCINOMA OF THE CERVIX

Section I

Introduction

A. Importance and Incidence.

Cancer threatens the ascendancy of all other causes of death. Its study engages the attention of workers in all fields of medicine and surgery, and education of both the medical profession and the public is the most essential part of the campaign for lowering the mortality.

Experimentation is going on at an ever increasing rate in many well-equipped institutions, and it is hoped the future will bring still more effective remedies. The change in treatment brought about by the last 15 years is striking. Crossen states, "the physicians now coming on can hardly appreciate the cancer situation of only a decade ago, and physicians who have not kept up with these revolutionary cancer developments are in no position to advise a patient with cancer of the cervix."

The treatment of cancer carries a greater responsibility than the treatment of ordinary diseases. It has been said that a considerable proportion of human ailments are "self-curative" if given time, but cancer does not belong to this class. In cancer of the cervix, only the judgment and skill of the physician stand between that patient and certain death within a very limited time. The patient's survival is determined largely by the physician's judgment in the choice of a remedy and the thoroughness in its application. Consequently it is with a profound sense of responsibility that the

doctor makes the selection of the treatment for the individual patient.

Cancer of the cervix is leading tuberculosis as the cause of death in women. In 1920 in the registration area of the United States the number of deaths from cancer was 111,569, or 95.9 per 100,000 population. Cancer of the female genital organs, causes 14.3% of all deaths from cancer. About 35% of cancers occurring in women are located in the cervix. Of malignant neoplasms occurring below the waistline, carcinoma of the cervix is the most frequent. Of 1779 cancer specimens examined in the laboratory of obstetrics and gynecology at the University of Pennsylvania, 827 or 46.43% had their origin in the cervix. Dietel and Steffan-Eisen found, among all gynecological admissions, uterine carcinoma made up 6.2% of ward patients and 3.9% private cases. Cancer of the uterus begins in the cervix in about 95% of the cases.

The average age incidence is between 45 and 50, but the number of patients under 35 desiring treatment is on the increase. A complete discussion of Incidence cannot be undertaken until the classification of the disease has been discussed. Thus more on this subject will be found in sections II, III and IV.

B. Scope of paper.

There has been an increasing volume of literature on carcinoma of the cervix, because of its importance. It is obvious that any attempt to review all the literature on this subject would be futile. To avoid this difficulty, an attempt was made to review chiefly the recent literature on the subject.

It soon became apparent this also was an impossibility in a paper of this nature. Thus the opinions leading from the work of the men in the world who are the leading authorities in this field will be stressed. The reports of these men embody all that has been done in the past and serves as a goal for others in the field. Of course, another difficulty arises here. The leading men in the field show an approximate mortality of 75%, while the country at large shows a mortality which is probably in the neighborhood of 90%. Published statistics relating to cancer usually express the best results.

In selecting those men recognized as authorities, an attempt was made to get a wide geographical distribution. Among those chosen are Healey of the Memorial Hospital of New York; Regard of the Institute of Radium of Paris; Heyman and Forssell of the Radium hemmet in Stockholm; Chambers of the Marie Curie Hospital and active in the "Eleventh Annual Report of the British Cancer Commission"; Ward of the Woman's Hospital of New York; Schmitz of the Mercy Hospital of Chicago; and Bowing and Desjardins of the Mayo Clinic. Others are quoted throughout the paper, but these various clinics stand out above all others.

The subject of cancer of the cervix is such a complicated one and presents so many clinical and pathologic variations, and special problems in adaptation of the details of treatment to the individual case that it overflows tabular analysis. As the physician treats and observes patients day by day, endeavoring to give each patient the benefit of experience gained in preceding cases, his conclusions and prac-

tice are influenced by many things, which cannot be presented in a statistical form.

In the continual search for improvement in the treatment of the cancer of the cervix uteri, gynecologists welcome help from every source. If there is any modification of method that will really give the patient a better chance to survive they are anxious to use it. However, hopes are so often raised by claims that later prove to be mistaken, that any change from a tried and reliable technique must be made only after a critical analysis has shown definitely the superiority of such modification. An attempt will be made to relate the various methods of treatment accepted at the present, giving their qualifications, pointing out their faults and giving results, and comparing the various methods. Finally the problems of the future in the management of this disease will be considered.

Carcinoma of the cervix is divided pathologically into squamous cell carcinoma arising from the stratified squamous epithelium of the portio vaginalis of the cervix, and adenocarcinoma arising from the glandular columnar epithelium lining the cervical canal. Both of these tumors will be included in the paper. The incidence of squamous carcinoma is about 95% of cervical malignancies, and adenocarcinoma 5%. A variation in their response to treatment will be discussed in section IV. No attempt will be made to discuss the pathology of these tumors other than has been mentioned here.

C. Prophylaxis and Early Diagnosis.

In studying the treatment of any disease, the prevention naturally enters in as an important part. Especially so in

carcinoma of the cervix. Various authors quote the incidence of "advanced cases", by the time the patient seeks medical advice, as between 65 and 80%.

Cancer of the cervix is one of the most easily recognized malignant lesions, but unfortunately the patient is frequently unaware of any pathology until it is in the late stage. A number of other factors lead the patient to neglect seeking medical advice early in the disease. Among the most common of these are the inherent fear of cancer and the common belief that it is incurable. Also the fact that a discharge of some sort has probably been present for years, for it will be seen that cancer of the cervix rarely develops in a normal cervix. A slight alteration in the character of the leukorrhoea may be overlooked or regarded as of no moment. Atypical bleeding is often attributed to a menopausal disturbance. The chief reason, however, that patients delay in seeking medical advice early is probably the painless character of the early symptoms. Incomprehensible as it may seem, one of the reasons why a physician fails to recognize the disease is his failure to make a pelvic examination.

The more thoroughly the disease is studied the more evident becomes the necessity of early diagnosis. During the late stages the diagnosis is made without difficulty, but during the early state diagnosis is attended with uncertainty and positive recognition of the disease without the aid of the pathologist is usually impossible. In order that any early diagnosis may be reached the patient must submit to a physical examination.

by a physician who is capable of recognizing the disease, or who it, at least, sufficiently familiar with malignant conditions to become suspicious that cancer may be present, and who will take immediate steps to exclude or confirm the diagnosis.

Earlier diagnosis may be made more frequently in the future as more and more patients with non-malignant cervical lesions are being referred to the clinics by their physicians who regard the lesions as possibly malignant. This careful scrutiny and cautious attitude by the attending physician toward abnormal cervixes should certainly lead to more prompt recognition of the disease when it is present. On the other hand, proper therapeutic measures directed toward the cure of benign cervical lesions may also be expected to reduce the incidence of cervical cancer.

It is estimated by various authorities that 90% of cervical cancers have origin in lacerated cervixes. It is the cervicitis which develops after the laceration which is important. Hunner subjected 2895 cases of chronic cervicitis either to amputation or cauterization and found after a follow-up of ten years not a single case of cancer developed in this series. Combined statistics of Pemberton, Smith et al, Smith, Bland, and Graves, show that 18,562 patients treated by surgery and diathermy for cervical lesions only 15 subsequently developed cancer. The same authors quote statistics which show that of 2,255 patients with cancer of the cervix, only 32 had received adequate treatment of chronic cervical lesions.

The percentage of cures in early cancer of the cervix, as borne out by no less than 8 prominent clinic centers, ranges

from 64 to 80 per cent, emphasizing the importance of early diagnosis.

The early findings are purely objective and can only be found by examination. When subjective symptoms of pain, hemorrhage, and excessive discharge are present, it is the beginning of the end rather than the beginning of the disease.

Two things are primarily needed; first, a clearer knowledge of the histological appearance of cancer; and, second, some simple test by which the latent area may be located for the purpose of biopsy.

The work of Schiller of Vienna stands out in this direction. He noted that cancer of the cervix began in leukoplakia-like areas. He also noticed that while many of these areas could be discovered by careful search with the colposcope, it was impossible by the naked eye to distinguish cancer leukoplakia from hyperkeratotic leukoplakia, though such differentiation can be made by histological examination.

In discussing the pathology of a chronically infected and eroded cervix, it is important to bear in mind the anatomy, especially the histology of the structure. That portion which is seen through the speculum is covered with squamous epithelium, and is pink, smooth and glistening. Under the microscope it resembles skin. This epithelium ends just within the external os. The cervical canal which cannot normally be seen, is lined with a single layer of columnar epithelium, dipping down into the substance of the cervix to form glands. These glands have a normal secretion which gains exit through their mouths into the canal, thence into the vagina.

When infection gains entrance through the undamaged canal or through fresh lacerations, it goes deeply into the fibrous tissue as well as the glands. The acute infection brings forth a polymorphonuclear exudate, but in chronic disease, lymphocytes and plasma cells predominate. In such conditions there is an abnormal and irritating secretion from the glands which constantly bathes the outer surface of the cervix. The squamous epithelium around the external os cannot live in the presence of this irritating discharge and consequently an ulcer or erosion develops, resulting in a denuded, infected area, the typical angry red ulceration as seen through the speculum. This is the first stage of cervical erosion, and is referred to as simple erosion. In the course of time this raw area becomes covered in whole or part by columnar epithelium growing down from the cervical canal. It is interesting to note that the columnar epithelium grows in the presence of the irritating discharge and covers the raw area resulting from the death of the normal squamous epithelium. A function of proliferating columnar epithelium is to form glands, and therefore, glands develop where they are not normally found. When the ulcer or erosion becomes covered with the columnar epithelium the process becomes the second stage of cervical erosion. The appearance through the vaginal speculum is quite the same as that of a raw ulcer. In some instances it has a papillary appearance, "papillary erosion", or it may harbor distended cystic glands, the so-called follicular erosion.

Eventually as the severity of the infection becomes attenuated the squamous epithelium begins to grow back in its normal place, and there is developed the third stage of the erosion or healing stage. It is in this stage that some interesting and most important behavior of the epithelium is seen in microscopic study. The regeneration of this epithelium does not progress unmolested, for it is subjected to constant irritation by the persistently underlying infection. Due to intercurrent exacerbations of the infection the process suffers interference and the phenomena may be viewed as a battle between the squamous and columnar epithelium, as the infection fluctuates. As the result of irritation there is an abnormal growth of the deeper layers of the squamous cells which is evidenced by the formation of fingerlike projections or elongations of the rete pegs extending down deep into the fibrous stroma. As the squamous epithelium creeps over the erosion it often not only covers the mouths of the newly formed glands, but may actually grow down into their lumina. Under the microscope such a picture may so closely resemble carcinoma as to confuse all but the most expert pathologist. Bailey of Manchester, England, has shown in a most convincing manner the relationship of this particular phase of cervical erosion to carcinoma. From his series of 850 chronically infected cervixes, studied in serial section, he concluded that the constant irritation of this squamous epithelium caused it first to respond by the production and over-production of normal cells leading to the elongation of rete pegs, and that finally the normal reproductive

power is lost and replaced by the development of abnormal cells of cancer. These abnormal cells, of course, are embryonic epithelial cells and have all the characteristics of malignancy. He has seen very early malignancies in cervixes removed by amputation in which no malignancy was or could be recognized clinically. If his contribution is accepted, the belief based on years of clinical experience that carcinoma of the cervix is a sequel to chronic inflammation of the cervix will be confirmed.

Freedman (1934) says, "Histologic study of uterine cervixes has demonstrated the fact that a pre-cancerous, or what may preferably be called a carcinoid state, does exist before the actual development of cancer. There seems to be no doubt that cancer can be diagnosed from cell changes alone, even when no other criteria are present. The cancer cells present definite characteristics. The nucleus may show an increased chromatin content and abnormal mitosis, and the nucleolus may be relatively increased in size as compared to the rest of the cell. Although unassailable histological criteria for carcinoid conditions are not to be had, there still is a satisfactory means of diagnosis of this condition in the cervix. (a) The general appearance is not suggestive of established cancer. (b) Very few cancer-like cells are present and these are single and detached. (c) These altered cells are surrounded and separated by many normal cells. (d) There is very little or no loss of polarity. The attitude that cancer may be simulated perfectly histologically by a benign lesion is a mistaken and dangerous one."

The Schiller test offers a suitable method for differentiating actual early cancers from carcinoid states. His conclusions may be summarized as follows:

1. Cancer of the cervix starts in the squamous epithelium of the portion near the os and at first spreads superficially.

2. It always starts in unbroken epithelium and not in ulceration.

3. Histologically the chief determining points in diagnosis are, first, the oblique line of demarcation between the normal and abnormal areas; and, second, the anaplastic atypia and polymorphia of the abnormal cells.

While the Lugol Test is of greatest clinical value, there are various factors which may obscure it, so that while a positive test may not always be made without a microscope, a negative test is specific for the absence of carcinoma.

This test is dependent on glycogen in the epithelial cells. This is not the same as liver glycogen, and is present only in the normal superficial epithelium of the vagina and normal portio vaginalis of the cervix. It is not present in the cells of the canal, nor in scars, nor in those areas of keratinization with hyperplasia which cause the mucous membrane of the cervix to resemble epidermis. Having located a suspicious area of keratinization, that is, an area which does not take the iodine, a histological examination is then made of this portion.

For obtaining material for biopsy a punch is used if there is apparent ulceration, or if no ulceration, a rectangu-

lar diathermal knife. By this latter method a clean cut with a sufficiently large section including the entire thickness of the cervix is obtained. Two or three sutures are placed and the area heals rapidly, there having been no danger of implantation and no risk of infection or dissemination by open lymph or blood stream, the diathermal knife sealing as it cuts.

Therefore, it is important to remember that early in the disease the changes are confined to the epithelium. One no longer looks for breaching through the mucous membrane. It is therefore imperative that the microscopist take into consideration the character of the epithelial cells above everything else to arrive at a correct diagnosis.

The importance of treatment in the early stages of the disease is illustrated by the following facts. Out of a total of 507 patients seen by Whitehouse (1934) in England, only 34 sought treatment when the disease was in the incipient stage. The borderline cases numbered 86, and 387 were hopelessly inoperable. Of the 34 cases, 20 women were alive and well at the end of five years, or longer, a curability of 58.9%. Compare this with 6.7% and 10.6% in his cases in inoperable and borderline groups.

Whitehouse states, "It is good to treat cancer and cure it, but it is better to prevent it". He advocated improvement in investigation and treatment of the pre-cancerous cervix. "The lacerated and chronically inflamed cervix so often a neglected legacy of child birth, is a condition fraught with

the greatest danger. The total curability rate figures are not likely to be improved a great deal without the better cooperation between general public and the medical profession to ensure the earliest recognition and treatment of the disease".

Certain institutions have been able to educate their clientele to such an extent as to obtain a large percentage of the first, and second stage cases, as evidenced by Regaud's series showing 37% and Ward's series showing 60% in contrast to 23% average of other series. This is an encouraging fact which contradicts the assertions seen in literature that cancer educational efforts produce no tangible results. "This splendid showing in regard to the percentage of early cases by the Radium Institute of Paris, and the Womans' Hospital of New York, constitutes a pointed lesson to get busy in carrying out an effective educational program among the laity" says Crossen of St. Louis.

Von Franque (1933) paid high tribute to Hinselmann and his associates at the Hamburg clinic for their efforts at cancer control by searching for the pre-cancerous lesions. They examined 13,000 women colposcopically in 1932, some with discharge and bleeding, others (majority) attending the hospital for other complaints, or in response to sensible propoganda. His clinic is also attended by many young graduates who apply his methods on taking up practice. He cites an instance of a general practitioner who had attended the Hamburg clinic for two weeks and on returning to his practice had made a colposcopic examination in 200 cases; he had found leukoplakia in

five, four in women over 40 years of age. In all five the cervix was amputated, and in two, outspoken carcinoma was found.

Guggisberg (1934), at the University Woman's Clinic in Bern made an attempt to determine the relation between delay in securing adequate treatment and the clinical stage of the tumors when first seen. He found that in patients seeking medical advice within the first two months a large proportion of the growths were already inoperable. 21 of 72 patients who sought treatment relatively early were inoperable. It must be concluded from these facts that a large proportion of cancer of the cervix cases are fairly well advanced before symptoms become manifest. In fact, bleeding must be dependent on injury to the invading tumor or to partial degeneration of the growth. It is obviously true that a latent period exists between the inception of cervical cancer and the production of symptoms.

For this reason organization of cancer control by educating the public concerning subjective symptoms of uterine cancer is insufficient. The only way that early and symptomless uterine cancers can be discovered is by routine semi-annual examination of the patient in the cancer age. This work must necessarily be done by the general practitioners. They will be the backbone of the crusade for the early diagnosis of cancer. Their work will be complete only when they have taken the responsibility of referring patients with suspicious lesions to institutions equipped for the special surgical and radiologic care of these diseases.

Section II

Classification

In a paper on the treatment of carcinoma of the cervix it is essential to include a discussion of the classification of the disease, because, as it will be seen later, a great deal of the choice of treatment as well as prognosis and comparison of results depends on an accurate classifying of each lesion. It is also seen to be important in studying the incidence of early cases and studying the value of educational efforts. It assumes an important role in a majority of the literature on the subject. Its actual importance is questioned by some and stressed by others. At present its value remains an active subject for debate.

There are two chief methods of classification of this disease, namely (A) Clinical Grouping as to stage of the disease, and (B) Histo-pathologic Grading.

A. Clinical Grouping.

Healy (1933) states, "The crux of the problem from the standpoint of favorable results or cure, is the same in radiation therapy as in surgery and depends chiefly, so far as we are able to discern, upon the clinical stage of the disease." Thus its value is seen and will be seen further as the viewpoint of other men is expressed, and the end results are studied.

There are two separate methods of Clinical Classification in use in this country today. (1) League of Nations Classification as adopted by the League of Nation Cancer Com-

missions, and that of (2) Schmitz of Mercy Hospital in Chicago. The latter was adopted first and gained more or less general usage as Dr. Schmitz has been a frequent contributor to the gynecological literature for some few years. The former is creeping into more general usage, especially with the radiologists, and since treatment of cancer of the cervix is chiefly a radiological problem, it seems that this classification should be adopted.

(1). League of Nations Classification.

At the conference in Geneva, which reported in 1929, the following classification was adopted, and it has been accepted by the majority of clinics. The National Radium Commission has made it a rule that any institution hiring radium from them must keep its records in a definite form and classify the extent of growth, according to the following form:

1. The lesion is definitely a surface one. It is limited to the cervix, with no paracervical or parametrial fixation. There is free mobility of the uterus.

2. The deeper structures are infiltrated or there is an invasion of the vaginal wall or some slight paracervical or parametrial involvement. The uterus retaining some degree of mobility.

3. Extensive paracervical and parametrial involvement with complete fixation of the uterus.

4. Distant metastases or extension with invasion to the surrounding viscera.

Crossen (1933) states, "The League of Nations Classification should be used universally. A uniform international

classification of cases is imperative for comparison of results of different methods. This classification is satisfactory; it is already in rather general use, and is the only classification likely to come into general use."

He continues with, "In the case of each patient, the evidences of the extent of involvement should be worked out sufficiently to permit accurate assignment to class. Accuracy is enhanced by deciding definitely as to the class at the time of examination and then recording the decision. This obviates the difficulty encountered when trying later to classify a borderline case with some detail missing."

It is usually possible to say whether the growth has extended beyond the cervix, although care must be taken not to mistake inflammatory induration in the broad ligaments for malignant growth, thus putting the lesion in a more advanced stage than it really is, and when a "cure" is obtained recording that as curing an advanced state, thus improving one's statistics.

(2) Greenough Classification.

The surgeon practicing hysterectomy only needs to know whether the case is or is not too far advanced for him to excise the whole growth. Weibel, as it will be seen later, is one of the foremost perpetrators of the Wertheim School for radical excision. He uses the classification adopted by Greenough, which is accepted by the American College of Surgeons.

1. "Cases in which the neoplasm is very incipient and can be differentiated frequently only microscopically.

2. Cases in which the neoplasm has spread out some, but is still confined to small areas of the cervix. (Operable -- good prognosis.)

3. Cases in which it has spread to the adjacent vaginal wall or the parametrium. (Unfavorable but sometimes operable.)

4. Cases in which the urinary bladder, ureters, or rectum is invaded by the neoplasm. The uterus has become fixed. (Very unfavorable case, perhaps in some instances still operable.)"

Then they speak of the "Inoperable cases in another group which may often be successfully treated by irradiation, and finally the incurable case, for which there is a present no method of treatment available."

It is evident, their cases in the higher groups are much earlier than in the other methods of classification. The futility of attempting a comparison unless the group is understood is therefore very apparent.

The radiologist cannot use this classification because it would be of little value to him in comparing the different radiological techniques. One clinic might have a very large percentage of cases which were extremely far advanced, while others might be treating cases that were only just inoperable.

The discussion of the classification in relation to the results obtained by surgery and radiotherapy will be taken up later.

(3) The Schmitz Classification.

Here also the extent-of the growth is expressed in four

clinical groups, but they differ from the former.

Group 1. The clearly localized growth. It is on the average about one centimeter in diameter in all directions.

Group 2. The doubtfully localized growth. It is characterized by an edema or infiltration of the paracervical connective tissue and hence a decrease in the degree of downward displacement of the uterus.

Group 3. The invasive growth. It is marked by definite invasion of the parametria or regional lymph nodes, but the invaded structures are movable, though movability is decreased, due to loss of elasticity of the tissues of the parametrium.

Group 4. The fixed and terminal growth. It is distinguished by the fixation of the tumor, due to invasion of the deep visceral and parietal pelvic fascia, or invasion of the vagina, urinary bladder or rectum, or the formation of distant metastases.

Ward (1933) has made an effort toward bringing American statistics on cervical cancer into a form which a more direct comparison with European figures is possible. Thus he made a comparison of the two above classifications, showing the incidence of each, in his series at the Womans' Hospital in New York

	Number	per cent
Total cases	357	100.0
Operable (limited to cervix)	77	21.6
Group I (Schmitz) Stage I (League of Nations).	4	1.1
Group II (Schmitz) Stage I (League of Nations).	73	20.5
Inoperable (extended beyond cervix)	280	78.4
Group III (Schmitz) Stages II & III (L. of N.).	249	69.7
Group IV (Schmitz) Stage IV (L. of N.)	31	8.7

B. Histopathologic Grading.

Considerable attention has been paid to the study of cellular differentiation as indicated by variations in histologic structure. Here the pathologist is very important. His role is somewhat like that of the navigator of a ship. The navigator with his nautical instruments plots his course, thus assisting the pilot in guiding his ship.

Healy (1934) remarked, "Biopsy is essential not only to establish diagnosis but to establish prognosis, since the histologic type is a fairly accurate index of radiosensitivity." Various other opinions on this subject will be discussed later, as will the principle behind the theory.

The subject has attracted wide attention since Broders (1922) showed in squamous cancer, that the success of surgical treatment was closely related to the type of growth and degree of cell activity. In cancer of the cervix particularly, the marked differences which occur in structure have led to many attempts to trace a relationship between the histologic type and the clinical progress of the disease.

Some of the results and a mention of the technique of this investigation, will of necessity have to be included in this section of the paper. It properly belongs in other portions, but in order to study the value of the "malignancy index" and response to radiotherapy, and thus to see the actual value of the exhaustive attempts to classification, they will be included here and reference to them be made later in the proper section.

The number of five-year cures reported by Broders (1922) for the most differentiated type of squamous cancer of the cervix treated by surgery was 53.33% as compared to only 9.57% for the most rapidly growing and least differentiated tumors. The corresponding figures given by Martzloff (1927) were 67.6% and 14%.

After radiotherapy Healy and Cutler (1928) found an equally important but different relationship, more cures being obtained with the anaplastic, rapidly growing tumors than with the highly differentiated and more slowly growing forms of cancer. Adenocarcinomata for many years has been considered by Regaud to be treated preferably by surgery because of their insensitivity to radiation.

Apart from the need of a large number of cases treated by a uniform method and followed for a sufficient time, a study of the subject is complicated by the difficulties inherent in the problem of classifying cancer growths into separate and clearly defined groups and by the fact that no method of grading has yet been generally adopted or accepted as satisfactory. At the present time since cancer of the cervix is treated almost exclusively by radiotherapy and not by surgical removal, the tissue available for histological study is necessarily limited. An extensive curetting is not deemed advisable, and the tissue sent for examination is generally quite small; it is often heavily infected with bacteria and inflamed, and may be largely necrotic.

The most important difficulty, however, seems to lie in the fact that various portions of the tumor may show differ-

ent stages of cell activity and one portion be called Group II and another portion Group III, etc. Thus it may always be seriously questioned whether the tissue is really a fair example of the general growth structure. However, that is what is present to work with, and realizing the inherent difficulties, attempts have been made to classify them.

In this connection Martzloff (1928), in order to study the value of biopsy material, examined 70 specimens of cervical cancer removed at operation and compared the findings with those from the tissue removed for diagnosis from the same cases. He concluded that in a third of the cases the examination of biopsy material would fail to indicate correctly the predominating cell type. In Chambers (1933) study he concluded the same, that is, almost the same proportion of cases were set aside as unsuitable for grading, namely 228 in a total of 678.

Method of Grading.

It is generally accepted that the main basis of any system of grading should be the degree of differentiation, defining as far as possible the comparative degree of cell activity. In malignant tumors at most sites it is possible to trace a gradual transition from highly differentiated and more slowly growing forms to completely undifferentiated and rapidly growing varieties. But in separating these kinds it is important to remember that the rate of growth of tumor cells may vary considerably at different places in the individual case, and cell activity is not always a safe guide in determining prognosis.

Chambers, full time pathologist at the Marie Curie Hospital in London (Oct. 1934), has done the most recent and most complete work on the subject and arrived at some important conclusions. He made four chief groups of squamous carcinoma on the basis of cell differentiation and general architecture. He discussed the previous important contributions and used them in deriving his method and conclusions.

In Grade I, all the typical cases of the adult squamous carcinoma were included. In this form the growth invades the cell columns of various size, often in single strands, but the habit of forming stratified epithelium is practically lost. Keratinization sometimes occurs, but is not common in cervical growths. Squames and pearls and basal cells are a feature of the structure. This type is easy to recognize.

Grade II includes the tumors composed of thin spindle cells resembling those of basal germinating layers.

Grade III includes all cases in which there is a clear tendency to form stratified epithelium, and contains 4 sub-groups, according to the decreasing extent of differentiation. In the sub-group "Keratinized" the surface layers of epithelium are transformed into sheets of keratinized squames, which may be in whorls. In sub-group "differentiated" most of the cells furthest from the basal layer are transformed into squames but without keratinization. In other cases the cells of this region are large and vacuolated but evidently not dividing or only very occasionally. A basal cell layer can usually be distinguished. In the sub-group "transitional", the architecture

of the epithelium is most like that of the normal mucous membrane of the cervix and vagina. The basal cell layer is distinct, and the gradual change from transitional to spinal cells can be made out. In sub-group "anaplastic", although there is still a formation of stratified epithelium, the cells have lost their squamous characters and are deeply staining; mitosis can be found in all the layers of the epithelium.

Grade IV includes all the anaplastic growths which show no formation of stratified epithelium. In these the tumor cells have no squamous characters and are apparently in active growth. They are round or fat spindle in shape, with deeply staining nuclei, and mitoses are common. In this grade are two sub-groups, depending on general configuration. In Grade IV A, the growth is arranged in alveolar masses with a fair amount of intervening tissue. In IV B, the tissue is a solid mass of cells with little intervening tissue and simulates a sarcoma.

The following table shows the percentage incidence of the different forms:

	<u>No. of cases.</u>	<u>Incidence in 450 cases.</u>
Squamous Carcinoma		
Grade I - Adult	68	15.01%
Grade II - Spindle	40	8.90%
Grade III		
Keratinized	10	
Differentiated	30	
Transitional	164	
Anaplastic	39	
Total	243	54.00%
Grade IV		
Anaplastic A	57	
Anaplastic B	42	
Total	99	22.00%

For comparison with the results of other observers, reference may be made to the following table. Grades 2 and 3 are grouped together. The close similarity of the final results with those of Martzloff, and Healy and Cutler, is significant. It indicates there are two groups easy to recognize, namely the adult and the anaplastic. If all the others are grouped together, three groups can be defined, and the percentage incidence of these three is fairly constant when a large number of cases are considered.

<u>Author and Method of Treatment</u>	<u>Histological Type</u>	<u>No. Cases</u>	<u>Incidence</u>
Broders (1922) Surgery	Type 2, $\frac{1}{2}$ differentiated.	23	8.54%
	Type 3, $\frac{1}{4}$ differentiated.	153	56.87%
	Type 4, not differentiated.	93	34.57%
Martzloff (1923-27) Surgery	Spinal	50	15.50%
	Transitional.	259	66.8%
	Fat Spindle	47	12.00%
Healy and Cutler (1928)- Radiotherapy	Adult	35	17.00%
	Plexiform	123	62.00%
	Anaplastic	42	21.00%
Schmitz and Hueper (1927) Radiotherapy	Spinous-with cornification	9	31.00%
	Spinous-without cornification	61	
	Round cell	106	47.00%
	Spindle cell	49	21.70%
Chambers (1934) Radiotherapy	Grade I	68	15.10%
	Grade 2 and 3	283	62.90%
	Grade 4	99	22.20%

Chambers entered into this classification particularly from the point of view of finding evidence to show to what extent, if any, the response of malignant tumors varies with their histological structure, and also of finding whether there was any evidence to support the prevalent idea that certain histological types are insensitive to radiation.

Regarding the age incidence of the various groups, Chambers has worked this out in his studies. His results may be summarized by the statement, "each group shows the well known influence of the menopause, with a marked increase in cases between the ages of 40 and 60. There is very little difference between the various histological grades except for Grade 4; in this there is some indication that the anaplastic growths are commoner in younger women. His graph shows a definite rise and fall some years before the others.

Regarding relationship of classification to duration of symptoms before treatment, Chambers states, "There seems to be no particular relation between the duration of symptoms and the type of growth. The duration of symptoms also seems to have no relation to the clinical stage of the disease; many cases in the most advanced stage had symptoms lasting less than two months, and some of the least advanced had the largest duration of symptoms.

In correlating the clinical classification according to Stage (as adopted by the League of Nations), Chambers showed that every histological type is represented in each clinical variety. Reference may be made to the following chart:

	(all sub-groups)			
	<u>Grade I-Adult</u>	<u>Grade II-Spindle</u>	<u>Grade III</u>	<u>Grade IV</u>
Nodular	12	18	56	14
Infiltrating	31	19	81	30
Ulcerating	20	11	50	27
Crater	5	4	12	8
Fungating	13	9	42	31
Cauliflower	3	1	10	7
Endocervical	7	5	15	1
Pyometria	4	1	13	1

Regarding the radiosensitivity of the various histological types of malignancy of the cervix, according to the classification discussed previously, Chambers' results at the Marie Curie Hospital are as follows. The method of treatment was a uniform technique and followed as closely as possible throughout. The method of radiation used and the dose applied are of primary importance, for the differences between the responses of cells of varying histological types to radiation tend to disappear as the dose is increased toward the limit which can cause the death of any living tissue. No modification of the dosage was made on account of histological structure. All cases diagnosed were followed with a full course of treatment in all cases where it was not contraindicated for other reasons.

The method used is a modification of the Stockholm technique, to be considered later. An attempt was made to improve on this by improving the distribution of the radium. Their cases have been treated chiefly without supplementary X-ray, with few exceptions. Although the method succeeds in treating carcinoma cells within a definite distance of the surface to which the radium is applied, it fails to treat more deeply seated growth cells or metastases in the pelvic glands. For this reason, also, when considering the response to treatment of growths of different histological types, the disappearance of the growth at the site treated is of more value than the ultimate result; a comparatively large number of the patients who die have extension to the pelvic glands or metastases and no local recurrence. Thus Chambers' inquiry was

chiefly to discover in how many cases the treatment caused the growth to disappear at the primary site, taking into amount the histological type.

The following tables give their results:

Results (local cures) according to Histological Grade and Stage of the disease.) Cases treated more than two years ago.

LC - local cure.
NLC - no local cure.

Histological type	Stages I		II		III		IV		Total	Percent	LC
	LC	NLC	LC	NLC	LC	NLC	LC	NLC			
Squamous.											
Grade I	1	0	6	1	21	11	1	3	41	65.9	
Grade II	2	0	7	1	12	4	0	3	29	72.0	
Grade III											
Keratinized	0	0	2	2	2	1	0	0	27	63.0	
Differentiated	0	0	3	1	10	5	0	1			
Transitional	7	0	21	3	43	18	6	6			
Anaplastic	3	0	5	0	7	4	1	4	126	73.0	
Grade IV											
Anaplastic A	1	0	4	0	13	7	1	2	55	66.3	
Anaplastic B	3	0	3	1	11	8	1	0			
Adenocarcinoma	1	1	11	0	15	8	0	1	37	72.9	

If the more advanced cases are considered separately, those of stage III, there is still not more than 15% difference between the various histological types and this is also evident when the results are considered as a whole. It is also seen there is no evidence that adenocarcinoma are insensitive to radium.

Results according to the Histological Grade and Stage of the Disease. (Cases treated from three to eight years ago.)

L - Living.
D - Dead.

Histological type	Stage I		II		III		IV		Total	Percent	L
	L	D	L	D	L	D	L	D			
Squamous											
Grade I	1	0	2	1	10	13	0	3	30	43.3	
Grade II	2	0	6	2	6	8	0	3	27	51.8	
Grade III											
Keratinized	0	0	2	1	0	3	0	0	22	27.3	
Differentiated	0	0	2	1	2	10	0	1			
Transitional	5	0	14	7	24	30	2	9			
Anaplastic	3	0	5	0	5	4	0	1	109	53.2	
Grade IV											
Anaplastic A	0	0	2	1	3	7	0	2	34	41.2	
Anaplastic B	1	0	1	2	6	8	1	0			
Adenocarcinoma	1	1	7	3	10	8	0	1	31	58.1	

Thus Chambers has done much to discover the actual value of this method of classification and seems to be a bit skeptical of its value.

Jarstad and Auer (1933) of the Barnard Free Skin and Cancer Hospital in St. Louis uphold this method of grading of malignancies of the cervix.

Adverse criticism of grading is sometimes based on the fact that different grades are to be found in different portions of the same tumor. To meet this criticism they selected only the most rapid growing portion of such tumors as a basis for their grading.

In defense of the argument that at different periods of growth there is a difference in the grade of the tumor, they state this may be due to a difference in the resistance of the host at different times. In defense of the argument that the personal equation plays a great part, they graded the tumors independently in over 300 cases with less than one per cent difference in judgment.

They showed that clinical grouping is far more important from a prognostic standpoint than histological grading.

<u>Clinical group.</u>	<u>Histological group.</u>	<u>Cases</u>	<u>Length of Life After Treatment</u>
I	Grade II	3	82 months
	Grade III	2	72 "
	Grade IV	1	15 "
II	Grade II	4	53 "
	Grade III	6	60 "
III	Grade II	19	29 "
	Grade III	17	30 "
	Grade IV	3	44 "
IV	Grade II	46	17 "
	Grade III	45	9 "

(They have no cases listed in Grade I in any clinical group, because the table is only for cases treated by radium and x-ray alone, and all their Grade I cases were in Stage I and II, and they considered these operable, and received radical surgical treatment.)

They do not believe that these figures signify that grading is of no value whatsoever in the study of cervical cancer, for there are facts not shown in the table. They observed that the immediate effect of radium on the more indifferentiated types of tumors is greater than the differentiated types. They found greatest immediate regression in Grades III and IV than Grades I and II, the clinical extent of the involvement being practically the same, and a like dosage of radium being applied in each case. This is added evidence of the greater radio-sensitivity of grade III and IV tumors.

It was also their observation that rectovaginal and vesicovaginal fistulae occurred almost always in carcinoma of Grade III and IV variety after treatment with radium. This fact is significant when it is known that the radium dosage was approximately the same in a large majority of the cases treated, so it could not be by mere chance that this occurred. Thus they advocate consideration of the Grade in selecting the dosage to be employed. Some Grade I and II carcinomas even found to be so radioresistant that 7000 mgm hrs. given over a relatively short period of time has caused little clinical regression, and yet they were dealing with a relatively slow

growing type of neoplasm.

Thus they feel grading is of decided value in the specific case of carcinoma of the cervix and that it may be the deciding factor in the decision to employ surgical treatment rather than radiation or vice versa.

Therefore, it has been seen that clinical grouping is of much greater value from a prognostic standpoint than histopathologic grading, but the latter still has its importance.

Section III

Treatment

(Introductory Statement)

In considering the treatment of carcinoma of the cervix and attempting to derive the best method, it might at first seem easy to decide statistically the controversy of surgery and irradiation therapy, but unfortunately such an enquiry is by no means simple at the present time. First is the difficulty of getting reliable figures. Only recently has there been concentrated efforts of "follow-up" systems in the large clinics. Even when one has the figures it is by no means certain that they refer to the same type of case. This has been explained in Section II, and it was seen there, comparison should be simpler in the future.

Another great difficulty, in comparing results of radiotherapy and operation, is the fact that the majority of cases treated by radiotherapy have already passed the stage where surgical excision is possible. To overcome this difficulty it has been suggested that the five year survival rate of all cases seen and treated by radiotherapy should be compared with the surgery, plus those seen and found inoperable. This suggestion is quite impracticable if the statistics of different institutions are to be compared, as the type of case coming to one institution is different from that attending another. When a gynecologist is well known for his skill in excisional surgery, the operability rate will be high, but in a clinic which has a reputation for benefiting even advanced cases by radiotherapy, the number of patients who present them-

selves in the early stage of the disease will be relatively small. In certain clinics the operability rate has been estimated during a few months or a year and this figure has been used in all subsequent arguments concerning the relative values of the two methods of treatment, and of course, the futility of this is readily apparent.

Thus it is seen the task is not so simple. There are still other difficulties in comparison of the results which will be considered later.

At the Memorial Hospital, Healy (1934) in a study of 1,574 cases found 12.5% were in Class I. If that diagnosis were correct, it would seem that a cure could be expected in all of these cases. Unfortunately, they received only 55% cure. It is evident the apparent early cases are not as favorable as they seem to be, as cancer cells have already begun to spread to other parts of the pelvis, and that is why there is at present a trend toward more accessory irradiation of the pelvis. It is important to realize that one seldom fails to cure the cervical lesion in favorable cases; as it will generally have disappeared in four to six weeks in nearly every instance, and the disease will seldom recur in or about the cervix. Within a year or two after treatment, however, some which were apparently cured early cases, will begin to suffer from pelvic and leg pain and it is too well known that this is due to metastatic cancer in the retroperitoneal glands, and cancer has continued to grow in spite of the treatment, and when pain appears it is beyond control.

Thus, Healy (1933) remarks, "The response of tumors is not always what we expect, and there are unexpected variations in local tissue reactions, as well as the constitutional reaction of the patient, not only to the treatment but to the disease. We are at times sorely disappointed because an apparently early and favorable case fails to do well, and on the other hand we are surprised and confused because some cases apparently far advanced in which a good result is extremely doubtful, will respond unexpectedly well to radiation and become a five-year apparent cure."

A word in regard to the choice of treatment, and the modern trend which will be borne out much more completely later. It is interesting to note how uniformly combined radiation is now used in the large clinics of the world. Carcinoma of the cervix seems to be almost entirely removed from the domain of surgery and to have become problems of radiation alone. There are still a small number of gynecologists of ability, more especially in central Europe, who continue to do the radical hysterectomy in their most favorable cases, but even in Germany radiation therapy is gradually replacing surgery. It must be realized that radiation therapy is relatively new and that the physical and biologic problems interwoven are not yet fully understood.

"Radiological treatment of cancer of the cervix has, since its first efforts, scarcely fifteen years behind it. During these years it has fought its way through difficulties apertaining to the technique of the treatment, no less than those of a financial and social order. Many have seen the

great expectations of a few years crumble and have retreated disheartened. That is the reason why there are only six clinics that are able today to submit a fairly large number of radiologically treated cases which have been under observation five years.", states Heyman (1927) of the Radiumhemmet Institute.

A. SURGERY

1. Historical Development.

The treatment of carcinoma of the cervix has been practiced for hundreds of years, and it has been stated that hysterectomy was performed for this condition as far back as 1600. It is definitely known that Sauter, in 1821 performed a radical hysterectomy. The methods of surgical treatment improved out of all knowledge from that date until 1898, when Wertheim first brought his method of radical hysterectomy before the profession. The technique has been followed up to date with very little change; with, however, a primary mortality of 30% having been dropped to 8% in Weibel's last five hundred cases. The improvement is attributed to better preoperative care, improved types of anesthesia and asepsis, as well as improved technical skill of these men in the larger clinics who do so many.

Even the most ardent advocates at present admit that surgery can probably go no further in radical excision. Owing to the ignorance of the patients and the present imperfect organization for ensuring early diagnosis, excisional operations can only be practiced in a comparatively small number, and it is a question whether even in this small number should surgery be the treatment of choice.

In the Schauta clinic in Vienna, the primary mortality is at present 3.4%, due probably to a better choice of patients, and due to the fact that they have a radium department in conjunction with their operative clinic for treatment of late II,

III, and IV degree cases. Weibel's mortality rate is an exceedingly low figure for the average surgeon to aim for. In his great series of 1,000 cases he has become probably the master of this type of operation. The primary mortality for his total series is 13.8%.

Inasmuch as there are no great surgical centers in this country, for this particular disease, with such a vast amount of material as the two just mentioned, there are not, and probably never will be, any comparative surgical statistics available. Radiation clinics in the United States are the only comparative ones with which we may deal.

The Ministry of Health of England (1927) report shows an average immediate mortality of the Wertheim operation as 17% and this is probably higher because surgeons with a smaller practice, and of necessity an inferior technique do not report their work as frequently as the more experienced and better known men.

2. Technique.

(a.) Wertheim operation, as practiced by Weibel.

In his discussion of the choice of cases for operation, he uses the Greenough classification, which it was seen, includes operable cases up to group IV. Thus his higher groups include much earlier cases. He considers them operable, under this classification, up to group IV, if there is no contraindication such as marked senility, marked cardiac insufficiency, advanced arteriosclerosis, general cachexia, extreme adiposity, or unwillingness on the part of the patient to submit to operation.

Before a date is set for the operation the patient is examined by an internist to determine whether the patient is in condition to undergo a radical abdominal operation, or whether vaginal operation is to be resorted to. If the uterus is not movable and its neighboring structures involved, operative treatment is not considered. Since the radical vaginal operation does not involve so much handling of the viscera as the abdominal, and consequently the patient suffers less shock during and after the operation, cases of early cancer, cardiac cases and cases of general debility, are operated after the technique of Schauta (described later). Many of the technical difficulties encountered in operating very adipose patients after the method of Wertheim do not present themselves in the Schauta method.

After admission to the clinic and after careful examination the patient receives frequent vaginal douches (mercury oxycyanid 1:10,000). Cardiac cases are digitalized, digalen being the preparation of choice.

Every case is cystoscoped to test ureter function and to discover any existing ureteral anomalies. An intravenous pyelogram is done.

The evening before operation the operative field is shaved and disinfected, the rectum and sigmoid cleaned with enemas, and veronal .5 gm. is given to ensure sound sleep.

In the morning before the operation, if any tumor mass presents itself in the vagina it is cleaned away with a sharp spoon and then the bleeding surfaces coagulated with a hot iron coagulating device, after which the vaginal vault is

disinfected with a green soap solution, and mercury oxycyanid solution, and then tightly tamponed with iodoform gauze. An anesthesia for this is not necessary since manipulation of the portio does not cause pain. The vaginal wall must be protected from the heat, however. One half hour before the operation the patient is given 1 cc pantopon (Roche) intramuscularly.

Anesthesia.

Lumbar anesthesia is used almost exclusively in the Weibel Klinik. 10% tropocain (Merck) which is marketed in 1 cc ampoules, or a newer preparation Panto-Spinocain, which causes analgesia for more than three hours is used.

Wertheim Operation.

Patient placed in lithotomy position on the table. Then prepared and placed in an exaggerated Trendelenberg position.

After midline laparotomy, partial detachment of the bladder is done, freeing the cervix from the bladder. During this procedure the bladder is held against the symphysis with an anterior vaginal speculum, and the detachment carried out by blunt dissection. Complete dissection of the bladder from the uterus is possible only after mobilization of the ureters and uterus.

Then the infundibulo pelvic and round ligaments are transfixed and severed bilaterally. The two surfaces of the ligamentum latum are separated with the aid of long dissecting forceps and the ureters sought. It can sometimes be detected by peristaltic waves going toward the bladder.

The exposed ureter is then followed to the point where it enters the parametrium. The operator now passes his forefinger along the course of the ureter, gathers the uterine vessels with the tip of his finger, which vessels he has in the meantime exposed with the aid of tissue forceps in the other hand, double ligates, transfixes, and severs them. Then the course of the ureters in the true pelvis can be followed to the bladder.

Then the rectum must be separated from the vaginal wall. The uterus is drawn sharply upward and forward. The assistant then draws the rectum ventrally, so the peritoneum may be cut through. Further dissection is done with a sponge in dressing forceps and with long curved dissecting scissors. The rectum must be dissected laterally from the parametrium and sacro-uterine ligaments, for if this is not done the rectum may be injured seriously.

The parametrium has been dissected free anteriorly and posteriorly and the ureters have been mobilized in the true pelvis; now the removal of the parametrium is begun, for which purpose the curved Wertheim parametrium clamp and parametrium curved scissors are used. They are applied close to the pelvic wall. Next the sacro-uterine ligaments are clamped as close to the sacrum as possible and severed, thus mobilizing the uterus more. Then pull uterus upward and strongly to the side to obtain a better view. In this position other parametrium clamps are applied close to the pelvic wall and the amputation of the parametrium completed.

The uterus and adnexae remain attached now only to the vaginal wall. The bladder and ureters are dissected free from the vaginal wall for at least 3 cm. below the portio. An assistant now removes the vaginal pack and the vagina is again swabbed dry. The vaginal canal is then hermetically sealed by means of the Wertheim vaginal knee forceps. By such means contamination of the operative field is prevented. The vaginal tube is then amputated and the edges clamped. The cut end is sewed with interrupted cat-gut in such a way as to arrest hemorrhage and a reefing effect of the cut edge of the vaginal wall is obtained.

After transfixation with silk, the parametrium clamps are removed from one side and gauze applied to the stumps to prevent parenchymatous bleeding, then the process repeated on the other side. A drain is placed into the vaginal canal. Then the raw surface peritonealized, using interrupted silk.

If any regional lymph nodes appear to be enlarged they are removed after the uterus has been amputated. Such glands are most often found at the division of the common iliac, less frequently at the obturator foramen, and even less frequently along the course of the common iliac and external iliac. Because of danger of infection and implantation, dissection is done instrumentally as much as possible.

The abdomen is closed in the usual manner, using interrupted silk throughout. The skin sutures are removed in eight days.

(b) Schauta Operation.

It is self evident that an operation by the vaginal route can not be as radical as the Wertheim operation, but if the paravaginal incision of Schuchardt is used, it is possible to remove a very large amount of parametrium. This incision is an exaggerated episiotomy incision, which begins on the sinistrolateral aspect of the vaginal wall, extends through the introitus, courses around the anus in shape of an arc, and ends short of the tip of the coccyx. The incision includes the deep muscles of the pelvic floor and when it is completed the vagina gapes widely, permitting a better view and easier accessibility to the operative field. It is self evident that when operating per vaginum the regional lymph nodes can not be removed, which is a serious disadvantage to this procedure.

100 cc $\frac{1}{2}\%$ adrenalin-novacain solution is infiltrated into the perineum and vaginal wall and around the portio, more to prevent hemorrhage than for anesthesia. Approximately 4 cm. from the portio 4 to 6 Kocher clamps are attached so as to circumscribe the cervix. At the periphery a circular incision is made. By blunt dissection a vaginal mauchette is formed which is stuffed with iodoform gauze and closed with heavy silk sutures. The carcinomatous portio is now well covered and the danger of autoinfection and carcinoma implantation is lessened markedly. The sutures of the vaginal mauchette remain long so the uterus can be directed in any direction.

The field of operation is now changed for a sterile one, including gowns, gloves, drapes, etc.

The Schuchardt incision is made and careful ligation carried out. Retraction of the vaginal wall is gained. Then loosen the rectum from the uterus without opening the pouch of Douglas and ligate and sever the sacro-uterine ligaments. Then the urinary bladder is dissected free. The lower edge of the latter lies in view, and is at first dissected from the uterus only in the middle for if the dissection is carried laterally it will be difficult to establish the exact position of the ureters later. The portio is now drawn upward and to one side. At the uterine angle thus formed will be found the uterine vessels. With the aid of the blunt curved dissecting scissors, the bladder, the uterine portion of the ureter, and the uterine vessels are exposed. The uterine vessels are now doubly transfixed and severed, and the remainder of the parametrium is then more accessible. The plica vesicouterina is now opened and held in place by sutures. With the aid of long fine hooks the fundus uteri is gradually brought to the front. The adnexae stumps are sutured to the cut edge of the vagina with heavy cat-gut. The opening in the parametrium is brought together with a few silk sutures in the center, and iodoform gauze strips are pushed through the lateral openings. Then the usual closing of both incisions.

The routine post-operative measures are carried out after both procedures.

3. Discussion.

The surgeon who has spent the greater part of his professional life in attaining skill and dexterity in excision-

al surgery, will probably get better results by this means than any other. Nevertheless, even in his hands there is still a large initial mortality amounting to about 10%. This mortality weighs heavy in the mind of the young surgeon against performing the operation, when he knows with radiotherapy the initial mortality in any stage is practically negligible, (figures later). Again, there is the undoubted fact that radiotherapy is making advances every year, whereas it is generally recognized excisional surgery is unlikely to advance further. If the patient knows that she will be obliged to undergo a very severe operation, or knows other patients with similar symptoms who did undergo that severe ordeal, she will be less likely to seek advice in the early stage of the disease. With the more general use of radiotherapy for malignant disease and other causes of irregular vaginal hemorrhage, it will become common knowledge that this symptom is cured without operation, and patients will more readily go to the physician at the beginning.

One argument against radiotherapy is that its present methods do not affect glands already invaded by carcinoma cells, and that a complete Wertheim does remove these carcinomatous deposits. On the other hand, in a series of 214 cases published in 1926, in which Wertheim hysterectomy had been performed, 34 died as a result of operation and in 14 of these (41.1%) the glands were not carcinomatous. There is some justification for saying these 14 lives might have been saved by radiotherapy.

Bonney, in his operations has found parametrial glands involved in 43% of his cases, and thus it is evident radiation therapy is under considerable handicap in endeavoring to increase the percentage of absolute cures. Lynch (1933) stated that in none of the cases in which he did a radical abdominal hysterectomy and found parametrial involvement did the patient live five years. Thus the advantage does not seem so apparent after all.

Weibel in his most recent communication, discussing surgery and irradiation methods, states in 1929, the operability of cases in his clinic was 70% and that 120 cases were radically operated, but no five year end results are mentioned. He questions if radiation treated cases will remain without metastases even after five years, more frequently than operated cases. All his patients after operation are given x-ray once or twice annually for a period of several years. The radiation is applied in several small doses for a few days to four or five fields. All inoperable cases were treated with combined radiation. He states post-operative radiation has definitely improved end results and that "absolute" results for Wertheim's original series (1500 surgical cases over five years) were 25.6%.

Weibel stated (1933), it was not his intention at present to abandon surgery. In milder cases he will do vaginal hysterectomy because of the danger of overlooking carcinomatous glands is comparatively slight, and the vaginal operation has a lower primary mortality. He will also use

this operation in advanced age, abnormal obesity, poor general health, etc. With these exceptions the abdominal operation is his method of choice as it permits a more extensive dissection of the glands, etc. and gives better results although its primary mortality is higher.

Healy (1933) remarks, "On the whole there is not as much radium available in Germany, and this may be an additional reason for the frequency of operation of early cases of carcinoma of the cervix." He continues with, "The occasional persistence of recurrence of a definitely radio-resistant lesion in a case of cancer of the cervix otherwise favorable for cure must be appreciated, and when such a case is met with, we believe it is much better to promptly resort to hysterectomy rather than wait for further radiation." Thus there is a place for histological classification as well as surgery.

To sum up, therefore: The argument in favor of excisional surgery by Wertheim's hysterectomy is the ablation of the carcinomatous deposits in the glands, and this alone can be the justification for an operation which has an average immediate mortality of 17%. The arguments in favor of radiotherapy will be given later.

B. IRRADIATION

1. General principles.

Radium and Its Disintegration Products.

In a discussion of the treatment of carcinoma of the cervix, which it is seen is chiefly a problem of radiotherapy, it is necessary to include a brief resumé of the principles

or radium and x-ray, and their action on malignant tissues. The following is by no means complete, but it is only intended the basic principles be given in order to complete the train of thought with that which is to follow.

Radio-activity.

Rutherford and his collaborators have established the theory that the atoms of certain elements break down to form new atoms, which possess physical and chemical properties quite distinct from those of the parent substances. During the disintegration of such substances a large amount of energy is released in the form of rays, and hence these substances are called "radio-active". Radium is an element of this type, but, although it is continually breaking down into bodies of lesser atomic weight, it takes approximately 1590 years for a given quantity of radium to lose half its activity. At the end of another 1590 years the value will have diminished to a quarter, and so on.

When isolated, radium is a white metal easily oxidized in air. It has an atomic weight of 226.5 and when it disintegrates one of the break-down products is, at ordinary temperatures, a gaseous substance called radium emanation, now perhaps better known as "radon". The other product of its disintegration consists of alpha particles.

The Alpha Particle.

The alpha particle given off from radium has a mass four times that of hydrogen and is really an atom of helium with a positive charge of electricity. It moves at a rate of 15,000 miles per second, and is stopped by its passage

through a few inches of air, or by any material as thick as a cigarette paper. The container of the radium is, therefore, certain to stop all alpha particles, and they are of no therapeutic interest.

Emanation, or Radon.

This gas can readily be drawn off from radium in solution; it has an atomic weight of 222, and chemically is an inert gas which becomes solid at the temperature of liquid air. There are several methods by which it is pumped off, but the principle underlying them is the same. The radium in solution is kept in flasks in a lead-lined safe and connected, by glass tubes passing through the back of the safe, to a mercury pump and purification plant. The pump first draws off the emanation and, after purification, compresses it into a fine capillary tube. The capillary tube can then be sealed off and placed inside the container. The radon thus obtained gives off alpha particles and breaks down into radium A.

Radium A, B, and C.

Radium A is a chemically inert substance and is reduced to half its value in three minutes, breaking down in turn into radium B and helium. Radium B breaks down into radium C and C₁, which in turn break down into other bodies of lower atomic weight which are of no therapeutic interest. With the breakdown of radium B and radium C, beta and gamma rays are emitted. The emission of an alpha particle lowers the atomic weight by 4, while the emission of a beta particle does not affect the atomic weight.

Although radium is continually breaking down into these bodies of lesser atomic weight, the first step in the breakdown occurs very slowly. Once, however, the emanation gas has been formed, its decay into radium A, B, and C is comparatively rapid. It is reduced to half its value in 3.82 days, and the life of radium A, B, and C is merely a matter of minutes.

Beta Rays - Beta particles are electrons travelling at a high velocity, which in some cases approaches that of light (186,000 miles per second). These beta radiations are of very great importance in radium therapy. Owing to the fact that they are more readily absorbed than gamma radiation, they cause much more effect on living tissue. Experience in the treatment of malignant disease has shown that their action is undesirable, and the radium must therefore be surrounded by a filter -- e.g. 0.5 mm. of platinum -- which will transmit gamma rays and yet stop the beta rays given off by radium B and radium C. The filter, however, is in itself a source of secondary beta radiation.

Gamma Rays - Gamma radiations are electromagnetic waves which have a uniform velocity but vary in wave-length, the shorter waves being more penetrating. When, however, the gamma ray passes through a substance, such as a metal container, it loses some energy by absorption, and at the same time its impact gives rise to a secondary radiation. This secondary radiation, which is very important in radium therapy, is made up of beta radiation and of gamma radiation of a longer wave-

length than the original gamma ray. The beta rays produce necrosis of tissues, and it is possible that some of the longest gamma radiations have the same effect. The secondary beta radiations can to some extent be absorbed by placing the radium container in a secondary filter of low density, e.g. rubber.

Radio-Active Equilibrium.

If radium is placed in a sealed container, the radiation passing through the walls of that container increases up to a maximum, and thereafter for all practical purposes remains constant. The time taken to reach the maximum is approximately 28 days. When this condition is reached, a state of radio-active equilibrium is said to exist. The explanation of this is as follows. The rate at which radium disintegration is constant and very slow, but the rate at which the primary disintegration product - radon - breaks down is comparatively rapid. Thus the rate of formation of the disintegration products is determined by the rate of decay of the parent radium and the amount of these products at a given moment is determined by the amount of the parent radium present. It is obvious that as soon as the radium is introduced into the container, a gradual accumulation of radon and its succeeding products of disintegration takes place. This accumulation continues until the rate of breakdown is equal to the rate of formation, and when this stage is reached the maximum amount of this substance is present.

Choice of Source of Radiation.

Since the therapeutic agent - gamma radiation - is obtained from a disintegration product of radium, namely radium C, it is obvious that either the radium element itself or the product radon can be used to treat the patient. When a salt of radium element is used in a container all the processes above described are going on within the container, and therefore there is, practically speaking, a constant source of radon, which produces radium C, which keeps the supply of gamma rays up to constant level. If, on the other hand, the emanation gas (radon) is separated from the radium element and used apart from the parent metal, it will rapidly break down into radium A, B, and C, and there will be no further supply to take its place.

There is at present some difference of opinion on whether it is more advantageous to use radon or radium. It is unlikely that this question will be finally settled until it is known whether a constant amount of gamma rays and long application are necessary for the treatment of tumors. If radon is used, the intensity of the gamma radiation diminishes to half its value in 3.82 days. Should, however, the duration of the exposure be limited to 24 hours or less, then radon can be used instead of radium element.

There are several advantages in using radon:

- (a) It can be obtained in a highly concentrated form by compression into capillary tubes, and it can be readily distributed in any desired amount amongst any number of containers of selected shapes

and dimensions.

- (b) In the form of seeds it can be buried and left in the body indefinitely.
- (c) The risk of loss of radium is reduced to a minimum, as the radium salt itself is never taken out of the safe.

The disadvantages of radon are:

- (a) Its output does not remain constant, but diminishes by 16 per cent per day.
- (b) Its use is only justified economically if a large amount of radium is kept in solution and the gas is pumped off frequently.
- (c) Its containers must be made and filled by a skilled technician.

Choice of Radium Salt.

The bromides and chlorides of radium are very soluble, whereas the sulphate is insoluble. For this reason radium sulphate is generally employed in platinum needles and tubes which are likely to be sterilized by boiling. At one time the more soluble bromide was used in these containers, but if any small crack or perforation occurred in the wall the contents were dissolved out during sterilization. When, however, the radium is to be a source of emanation, one of the soluble salts is used.

X-Rays and X-Ray Apparatus.

Although it is not my intention to describe x-ray treatment in great detail, yet it is essential for all in-

terested in treatment to know the elements of the subject, because the treatment of this condition requires combined radium and x-rays to obtain the best results.

Rontgen discovered the x-rays in 1895, and Leopold Freund, of Vienna, first tried them for medical treatment. It is probable that Sjogren, in 1900, was the first man to try to treat malignant disease by x-rays. In 1901 Straeter demonstrated that the skin was less affected by hard rays, i.e. rays of short wave-length, than by soft rays. In 1902 the first x-ray dosimeter was invented by Holzknecht. Since this pioneer work great strides have been made in x-ray therapy, and the instruments have been enormously improved. Speaking generally, the aim has been and still is to obtain rays of the shortest possible wave-length. The higher the voltage applied to the tube the shorter the wave-length produced; already 220,000 volts are used as a routine, and there is hope that this may be increased in the near future to 900,000 volts. Generators and experimental tubes for a million volts have been constructed, but the difficulty up to the present has been to make efficient tubes.

Principle of Production of X-Rays.

In order to produce x-rays it is necessary (1) to detach electrons from atoms, and (2) to project these electrons at a high velocity against a piece of metal; the sudden change of speed on impact of electrons against the metal target gives rise to x-rays. In order that the movement of the electrons may not be impeded before the impact, the operation is carried

out in a vacuum tube. To give the necessary velocity to the electrons a high-voltage current must be sent through the tube. The higher the voltage the greater the velocity of the electrons and the shorter the wave-length of the x-rays produced.

The voltage in the public domestic electricity supply is insufficient and therefore an alternating current transformer is generally used to "step up" the voltage, and thus 200,000 volts or more is obtained. The current flowing through the tube is made unidirectional by means of rectifying valves. A practically constant high voltage instead of a fluctuating one can be obtained by employing suitable condensers in the rectifying valve circuits.

The x-ray tube most commonly used is of the metalix type. The cathode consists of a spiral wire which, when heated to a red heat, gives off electrons. The anode is generally made of tungsten because of its high atomic weight and high melting point. As a rule the current used is small, being of the order of 4 milliamperes.

Filtration.

Since the shorter waves have been found by experience to be the most valuable in therapy, the longer wave-lengths are absorbed by filters of zinc, copper and other metals. The shortest x-ray wave-lengths now in common use, however, are more than double the length of the shortest gamma rays, and that is why efforts are being made to manufacture machines and tubes using 900,000 volts. Such instruments would produce

wave-lengths of the same order as the majority of gamma rays used in radium therapy.

Treatment by x-rays and treatment by radium are in no way antagonistic. On the contrary they are, in our present state of knowledge, complementary. The advantage of x-ray therapy is the greater intensity obtainable, and the large areas which can be irradiated. The great disadvantage is the difficulty of obtaining radiation of sufficiently short wavelength.

The Biological Action of Radium on Malignant Tissues Mitosis in Malignant Tissues.

Mitosis, which was plentiful before irradiation has entirely ceased when the radium was removed. Two or three days after the removal of the radium, mitosis returned, but was so abnormal as to be scarcely recognizable. The cells themselves had swollen to three or four times the normal size. The chromatin was scattered throughout the cell, and traces of the spindle were also found; sometimes three rudimentary spindles were noticed in one cell. This abnormal mitosis was present in a very large proportion of the cells--far more than in the tissues before irradiation. In some sections apparently normal mitosis was noticed, but this was rare. In no case was there evidence that the abnormal cells actually divided. At the end of seven days abnormal mitosis had ceased and the cells had begun to break up. In some cases the uterus was removed by hysterectomy at the end of six weeks, and sections showed no cancer cells. In hysterectomy done at a later period

there was considerable fibrosis, and in one or two cases islands of tissue, which might originally have been cancer cells but were now merely debris, were surrounded and isolated by fibrous tissue. This work has been repeated by others, and with the more adequate irradiation which is now carried out there can be very few cases where it is not possible to eradicate the growth entirely from the cervix.

Indirect Action.

These observations on the cells themselves cannot be taken as absolute proof that the action is direct, because at the same time that these changes take place in the cell, changes are occurring in the blood supply. There is usually an obliterative endarteritis which destroys the lumen of the vessels and may be responsible for some of the cellular change. This indirect action provokes the question whether or not an overdose of irradiation actually diminishes local resistance and increases the power of growth of the tumor. The Swedish school, in particular, hold the view that successful radiotherapy is a matter of restoring the balance of power in favor of the normal tissues; that any overdose to these normal tissues tends to diminish their power of resistance, and that the growth temporarily checked by the direct action may ultimately increase at a greater rate.

Todd suggests that the action of radiotherapy is more indirect than direct, and that this indirect action takes place (a) locally, at the junction of normal and malignant tissue, by stimulating defensive action, and (b) generally,

in those parts of the mesoblastic tissues which are concerned with the defense mechanisms, especially certain cells of the blood and the cells of the reticulo-endothelial system.

If radiotherapy depended purely on the direct action on the cancer cell, it would be reasonable to believe that every cancerous growth, whether large or small, could be made to disappear locally. This, however, is not true. A great difference is found in cancer in different sites, but in whatever site the cancer is situated, a large growth is much more difficult to eradicate than a small one. The opinion is undoubtedly gaining ground that the indirect action is of very great importance. The question of direct and indirect action is closely bound up with the subject of radio-sensitivity.

Radio-sensitivity.

This subject has been discussed briefly in Part II, but will be referred to again here.

That the different normal tissues of the body vary in their sensitivity to irradiation is well known. For instance, a nerve-fibre is practically unaffected even by large doses of radiation, whereas the ovaries and testicles are very sensitive. The factors governing radio-sensitivity are very imperfectly understood. The fact that quickly growing tissues are more radio-sensitive than more stable ones is well known, and was referred to by Bergonie and Tribondeau many years ago.

These observations, sometimes spoken of as the "Bergonie and Tribondeau Law" have frequently been misinterpreted to mean that a cell is radio-sensitive during the actual process of mitosis. Experiments show that this is not true, but that

cells will go through the phases of mitosis if the process has already started or is about to start when the radium or x-rays are first applied. It would probably be more accurate to state that when a cell is undergoing active metabolism (which leads to mitosis) it is more radio-sensitive than at other times, and therefore a tissue which contains a great many cells, in a state of active metabolism, is more radio-sensitive than a quiescent tissue. The question whether individual cells isolated from different tissues, or from tumors which differ in their rate of growth, are all of different radio-sensitivity has not yet been completely answered. There is, however, some evidence in experiments recently carried out by Mottram that the cells from tumors which have different radio-sensitivity in the animal are themselves equally radio-sensitive in vitro.

Mottram has suggested that the radio-sensitivity of normal tissues and of tumors depends to a large extent on the blood supply, and that the greater the blood supply the less sensitive is the tissue. This theory is borne out by the experiments of Russ and Scott, who state that cells around blood vessels appear to be protected to some extent from the damaging effect of the radiation.

Clinically, there is no doubt that some tumors respond to radiation far more readily than others, and it is of the utmost importance that some explanation should be found for this difference in radio-sensitivity. Speaking generally, squamous-celled carcinomata respond more readily than columnar-celled carcinomata, and sarcomata more readily than either.

The degrees of radio-sensitivity, however, cannot be explained merely by the type of growth, because there are great differences of sensitivity in the same type of carcinoma in different parts of the body. For instance, among the most radio-sensitive may be quoted the squamous-celled carcinomata of the cervix, whereas a few inches away carcinoma of the vulva is very radio-resistant.

The three possible explanations for these differences are: (1) rate of growth, (2) differences in the response of the tissues surrounding the tumor (the "tumor bed"), and (3) differences in the radio-sensitivity of the individual cells. Many observers have accepted this last theory and have tried to correlate radio-sensitivity with the histological findings of the tumor. As far back as 1893 Hansemann pointed out that there was a relationship between the histological appearances of the tumor and its malignancy. The more anaplastic--that is to say, embryonic--the type of growth, the more malignant.

Radio-sensitivity of Glandular Metastases.

Another very important question is whether metastases in lymphatic glands are less radio-sensitive than the primary growth. Most men believe that they are. Other observers consider that there is no greater difficulty in making the secondary deposits disappear, but all agree that to prevent a recurrence in the glands is undoubtedly far more difficult than to prevent a recurrence in the primary site. These observations suggest either that the tumor bed formed by the gland tissue is itself so radio-sensitive that it is destroyed by

the radiation and therefore can play no part in limiting the rate of growth of the secondary deposit, or that secondary deposit is stimulated by lymphoid tissue.

Methods in General of Applying Radium

There are four distinct ways in which radium or radon can be applied:

1. Interstitial Irradiation.

By this is meant the implantation of radium or radon in the tissue to be treated. The radium is generally contained in platinum needles. This metal has certain advantages: first, it has a very great density and therefore a thin wall forms an effective filter; secondly, it does not oxidize easily. The radium is generally put into smaller sealed platinum cells before being placed inside the hollow needle. A great disadvantage of platinum is its high initial cost. For this reason gold or silver is sometimes used, or even rustless steel. Such needles can be sterilized by boiling, or by placing in antiseptics, but care must be taken not to allow any mercury solution to come in contact with platinum. The seeds usually consist of short lengths of capillary glass tubing sheathed in platinum or gold.

This interstitial method is very widely used in the treatment of such conditions as carcinoma of the tongue, lip and breast. Its object is to distribute the sources of radiation throughout the tumor, and thus to get irradiation as nearly homogeneous as possible. It has been suggested, however, that a danger in this technique is that lymphatic channels may

be opened up and malignant cells implanted in them. An additional danger is that of carrying sepsis from an infected growth into the deeper tissues.

2. Surface Irradiation.

In this technique the applicators are generally in the form of flat plaques which are placed directly on the skin and usually left in position for a comparatively short time.

3. Cavitory Method.

The applicator is put into one of the natural cavities of the body, e.g. the antrum of the nose, the vagina or the cavity of the uterus. The great advantage of this method is the fact that no tissues are disturbed, but its defect, at any rate in theory, is the unequal distribution of the radiation. The tissue near the applicator gets a very large dose compared with those at a distance.

4. Distance Therapy.

The fourth way of applying radium is to place it at a greater or lesser distance from the skin. When it is desired to irradiate a large area of the skin or the tissues immediately underlying it, the most convenient method is to have a wax mould about 1 or 1.5 cm. in thickness and to attach the radium on to the surface of this mould. When, however, it is desired to irradiate a portion of the body at a considerable depth below the surface, then it is necessary to have a large quantity of radium, e.g. 4 gm., at a greater distance from the skin. Such a quantity of radium is used in much the same way as an x-ray tube and, since the distance between the skin and

the tumor is generally less than the distance between the container and the skin, the intensity affecting the latter will be very little greater than the intensity affecting the tumor situated more deeply in the body. This large quantity of radium is often spoken of as a radium bomb, but the term "radium beam therapy" will probably be applied to the method in the future.

The Dose

When a clinician wishes to use radium, the first question he asks is: "What dose shall I give?" The word "dose" probably suggests to him the idea of a drug which will be distributed throughout the body and the action of which will generally be the same if the same amount is given. When, however, the term "dosage" is used in radium-therapy, no such simple idea can be envisaged. The quantity of radium that is applied does not by itself give any indication of the amount of energy the tissues will receive. The energy received will depend on many factors.

Distance Factor.

The most important of these is the distance of the radium from the tissues. In this respect the radiations from radium are similar to the radiations from a source of visible light. The intensity of the rays from a point source will rapidly diminish the further the point of light is away from an illuminated surface. This intensity diminishes inversely as the square of the distance from the source. At present, there is no simple practical method of measuring and recording the intensity of irradiation in the tissues.

Duration of Irradiation, or Time Factor.

The amount of energy which comes from the radium will obviously vary with the mass of the radium that is being used, but as the supply of energy from a given quantity of radium is continuous, the amount of radiation falling on the tissues will vary with the time that the radium is kept in position. To put it another way: the amount of energy that the tissues receive depends on the intensity multiplied by the time of exposure. As it is difficult to calculate exactly the intensity of irradiation at different distances from a container, the dose is frequently calculated by multiplying the mass of the radium used in the applicator by the number of hours during which the exposure is made, and the result given as so many milligramme hours. This method of describing a "dose" may be of some value where all the other factors are known, but by itself the statement that so many milligramme hours were given is of no value whatever. For instance, 1 mgm. of radium element may be used over 100 hours, or 10 mgm. may be used for 10 hours, or 100 mgm. may be used for one hour. The amount of energy received at any one point would be same in all these cases if measured by physical standards, but the results of that energy on living tissue would be very different.

Dimensions of Containers.

Since the amount of energy received by the tissues from a given amount of radium varies considerably with the dimensions and shape of the container, it is essential to give the exact dimensions of the containers used. In needles

it is convenient to have a standard amount of radium per unit length, e.g. 1mgm. per cm. length or per $\frac{1}{2}$ cm. length; the "active length", not the total length, is quoted.

Filtration.

As radiations pass through the walls of the container, certain components are filtered out. Practically all the beta rays from Radium B and C and some of the longer rays are absorbed by 0.6 mm. of platinum, for instance, and if greater thickness of metal is used, more of the gamma rays will be absorbed. It is, therefore, very necessary to note the thickness of the walls of the applicator and to record it in terms of the equivalent thickness of platinum or of lead.

When gamma rays hit a substance, particularly a substance of great density, e.g. the walls of a radium container, some of the shortest rays may pass through the substance, but others are absorbed and produce beta rays and gamma rays of a longer wave-length than the original rays. These secondary rays can be cut out to some extent by covering the container with a non-metallic substance of low density, such as rubber.

Common Filter Materials

Metal	Thickness in mm. necessary to absorb 99.9% of beta rays.
Platinum	0.6
Gold	0.7
Lead	1.2

Dosage of Emanation.

A different method of dosage is necessary for radon. The amount of gamma radiation decreases at a regular rate, and

at the end of 3.82 days the value has fallen to half. Another way of saying it is that the value falls off by 1/6th each 24 hours when separated from radium. Thus at the end of 3 days there is 58.2% of the initial strength, 6 days is 33.9%, 9 days 19.7%, 12 days 11.5%, 20 days 2.7%. The dose is expressed in the number of millicuries destroyed. A millicurie is the amount of radon present when one mgm. of radium has reached equilibrium. One millicurie destroyed is equivalent to 133 mgm. hrs. There must be a time element of exposure correlated also, because the biological effect is greater for a large intensity over a short time than if a small intensity is used over a long time, the number of mgm. hrs. being the same. The more highly differentiated growths also seem to require a longer exposure than the undifferentiated growths.

2. Radium and Radon.

The general principles have been described as they pertain to malignancies. Now an attempt will be made to describe the more specific techniques as they pertain to carcinoma of the cervix. The methods of the leading clinics where a large amount of radium is available, as well as a method which may be used with smaller doses of radium. First, a word in regard to the history of radiation therapy in malignant disease of the uterus.

(a) Historical Development.

The treatment of carcinoma of the cervix by radium dates back to about 1905; and even in those days, with very inefficient methods, the local growth was successfully destroyed in a certain number of cases. It is perhaps fortunate

that there are no organs in the immediate vicinity to which injury would cause immediate death. Thus the pioneers were encouraged to persevere, and in a sense, radio-therapy owes to gynecology its present position in the treatment of malignant disease.

The earliest cure of cancer by Roentgen Ray was reported in 1900 by Stenbeck. In a few months Johnson and Merrill reported eradication of a biopsied carcinoma by radium. In those early days glass containers were used, and therefore radiation consisted of both beta and gamma rays. In 1907 Dominici introduced containers made of silver, the walls of which were 0.5 mm. thick. Between 1909 and 1914 Cheron and Duval published statistics of 158 inoperable cases of carcinoma of the cervix treated by radium. In 77 of these the growth completely disappeared clinically. One died of an intercurrent disease 15 months after treatment, and autopsy proved beyond a doubt that no malignant disease remained. This is the first case in which it was scientifically proved that radium could cure cancer.

Professor A. Doderlein of Munich, has laid claim to be the first to have established the routine use of radium and x-ray treatment of cervical cancers. He began his work in 1913 and is still getting good results.

When radium was first used, the only cases treated were the advanced ones in which excision was entirely out of the question. When they saw considerable benefit was obtained, the same line of treatment was employed for less advanced cases. The next step was the treatment of patients whose growth was

technically operable, but whose general condition made excision inadvisable. The results were sufficiently promising to justify this treatment for patients who might otherwise have been treated by hysterectomy.

Since that time many variations in technique have been tried and are still being tried. The variations observed in different clinics of importance can only indicate that the detail of dosage, filtration, frequency of treatment, duration of time of application of radium, interval of time elapsing between treatments are still in a somewhat experimental stage and no hard and fast rule can be drawn regarding these details. To some extent these details depend on the amount of radium available in the individual clinic. Healy (1933) states, "The minor variations in technique now used in the different clinics apparently do not matter greatly so long as the cervix receives sufficient dosage with suitable filtration, and routine care is taken of the patient."

Techniques Employed

1. The Stockholm Technique.

One of the best known methods of treatment and one which has given very good results is that used by Heyman at the Radiumhemmet Institute in Stockholm. This is a cavitary application of radium. Heyman makes slight variations for individual cases, and has even introduced relatively big modifications in some series with the object of making comparisons. He states that in the majority of the cases from which his

statistics were made, the patients were treated on three occasions, but that more recently in a special series the number of applications was reduced to two. The second application is carried out one week after the first, and the third three weeks after the second. The patient is given a hypodermic injection of morphine, but no anesthetic. The cervix is dilated up and 40 mgm. of radium is inserted in the cavity of the uterus and cervical canal. In the vagina another 70 to 80 mgm. of radium element is placed in a number of tubes, generally in 2 or 3 boxes, according to the size and disposition of the growth, and kept in position by gauze plugging. The filter is equal to 1.5 mm. of platinum or 3 mm. of lead. The following typical series of treatments are given by Heyman as an example:

First treatment:

	<u>mgm.</u>	<u>hrs.</u>
In the uterus (4 tubes) 40 mgm. element x 19 hrs.	- 760	
In the vagina (10 tubes) 78 mgm. element x 19 hrs.	-1480	

Second treatment:

In the uterus (1 tube) 43 mgm. element x 21 hrs.	900
In the vagina (10 tubes) 71 mgm. element x 21 hrs.	-1490

Third treatment:

In the uterus (1 tube) 38 mgm. element x 19 hrs.	- 720
In the vagina (10 tubes) 80 mgm. element x 19 hrs.	-1520

Total dose in the uterus 2380 mgm. hrs.

Total dose in the vagina 4500 mgm. hrs.

2. The Paris Technique.

The following method of applying radium for the treatment of the primary growth has been in use for many years by Regaud and his associates at the Curie Institute of Radium. Careful investigations are made to see what organisms are present in the cervix. An attempt is made to clean up the growth by means of douches, and if there is no rise in temperature

during the first 24 hours, the cervix is dilated. If a streptococcus infection is present, particular care is taken to stop treatment on the slightest rise in temperature. If all goes well after the preliminary dilatation, and no fever follows in the next 24 hours, the radium is placed in position. The intrauterine stem applications contain 3 radium needles in a tandem of usually 3 sections, one containing 6.66 mgm, the other 2 sections contain 13.3 mgm. Vaginal applications are placed in cork tampons connected by a steel spring resembling a clock spring and called a colpostat, containing 33.3 mgm. of radium element distributed in 3 tubes, two of which contain 13.3 mgm. each, while the third contains 6.6 mgm., giving a total radium application of 53 mgm. The filter of the uterine tubes equals 1 mm. of platinum. In addition to this there is a rubber filter 1.5 mm. thick. The filter for the colpostat radium is 1.5 mm. of platinum. The cork acts as a secondary filter, and to keep the walls of the vagina away from the containers. This apparatus is kept in position by means of gauze plugging.

Quite recently the containers and technique have been modified. In the original technique the radium was kept in position for 5 - 7 days, the containers being removed, cleaned and replaced daily. In the more recent technique, the vaginal containers are placed in position for three days before the intrauterine application is carried out. During the next four days both the intrauterine and the vaginal applicators are kept in position. The first treatment with radium is always

under an anesthetic, and is followed in 12 to 21 days with deep x-ray treatment.

Regaud's statistics show a high cure rate and his method has attracted much attention. The theory of the method is to give each generation of cancer cells a dose of radium at the stage of cell division when they are most radium sensitive, and this is supposed to be accomplished by spreading the dosage over from 5 to 8 days as he does.

3. Technique Employed in America.

Those of (a) The Memorial Hospital, (b) Johns Hopkins University, (c) Technique of Michael Reese Hospital and (d) The Mayo Clinic will be given. In America the cavitory applications are generally employed, but in a few clinics seeds of emanation are placed around the growth in addition to a tube of radium placed in the cervical canal.

(a) At the Memorial Hospital, New York, large quantities of radium are used for local treatment, but kept in position for a very short time. In addition, Healy (1933, 1934) has placed much stress on deep x-ray therapy preliminary to radium application. The patient is admitted and, after the vagina has been cleaned as much as possible, the x-rays are given, followed immediately by radon treatment to the vagina and the uterus. The general procedure is to use radon for 3000 milli-curie hours in the body and cervix, the exact quantity varying slightly and the time varying from 12 to 24 hours to correspond. The radon is contained in a tube of gold, the walls of which are 0.5 mm. thick. There is a secondary filter of rubber. The

3000 millicurie hours are divided into 1000 in the upper part and 2000 in the cervix. In addition a "bomb" containing from 1000 up to 1500 millicuries is placed in the vagina, generally in three different positions. This "bomb" consists of a lead cup, the walls of which are 1 cm. thick. The open end of the cup is directed into one lateral fornix, then into the other lateral fornix, and lastly up against the cervix itself, for one hour in each position.

If the cervical lesion fails to disappear in 4 to 6 weeks Healy resorts to interstitial radiation, usually by means of gold filtered radon seeds. If the response to this treatment is not satisfactory, and at the end of a month or six weeks it would appear there is still a bulky cervix due to the persistence of cancer, it is evident one is dealing with a radio-resistant lesion. Healy feels further radiation in such a case will lead to disaster by causing extensive necrosis and sloughing of tissues, whereas a simple abdominal hysterectomy at this stage may permit complete healing of the vaginal vault, and while the patient lives she shall be free from foul vaginal discharge, hemorrhage and fistula, but of course, will not be cured of cancer.

Crossen (1933) of St. Louis, decided in favor of giving full dosage in a single treatment. Supplementary x-ray was also used. He includes all cases for radiation therapy and none for surgery. He also gives part of the x-ray treatment before radium application. He states, "As far as American work is concerned, the full dosage near the beginning shows better results than the spread-out dose, in statistical analysis.

Thus, as it has been seen before, he upholds the value of histopathological grading, as well as surgery for some cases.

(b) At Johns Hopkins Hospital, large intensities are also employed for short periods of time. For the local conditions a tube containing 1 gm. of radon is placed in the cervical canal and another containing 2 gm. or possibly 1500 mgm. in the vagina; these are held in position for one hour. In addition to this a "bomb" or x-rays are applied outside the pelvis. The "bomb" contains 4 gm. and is applied at three different portals anteriorly, and three posteriorly. It is kept in position for four hours over each portal at a distance of 10 cm. Thus each portal receives 16 gram hours. X-rays are applied at a distance of 50 cm. at a tension of 220 KV and through two or three portals, each measuring 7 x 7 cm., with a filtration of 1 mm. of copper plus 1 mm. of aluminum. An erythema dose is obtained in about 15 minutes.

(c) Michael Reese Hospital of Chicago. Dr. Cutler, Director of the Tumor Clinic at this institution, 1932, published an article on the treatment of carcinoma of the cervix with small quantities of radium, pointing out the medical and economical advantages of this method as compared with the use of much larger quantities.

Donaldson (1933) states, "Radiation therapy can be successfully carried out with 50 mgm. of radium element, although it is desirable to possess 80 to 100 mgm. Quantities of radium from 3 to 5 gm. such as Regaud, Forsell, etc. have at their disposal must of necessity remain exceptional amounts.

But this fact is not of great moment, for the excessively large amounts which are used for percutaneous radiation can always be replaced by deep x-ray therapy. The use of such large amounts of radium means in reality the dissipation of large amounts of radiation energy. If the available radium in the world were collected and held in such large quantities it would necessarily limit the number of patients who could receive its benefits. Excellent results are obtainable even with comparatively small amounts of radium when properly used."

While it is true that gamma rays from radium are definitely harder than those which emanate from x-rays, it is a biologic fact that either type of gamma rays can be made to destroy carcinoma cells, or in fact, any cells in the human organism.

The American College of Surgeons special committee on the treatment of malignant disease, recommends the establishment of clinics throughout the country and advises the acquisition of at least 200 mgms. of radium distributed in small quantities such that the different tubes can be used in the treatment of all various forms of malignancies.

The cost of large quantities is prohibitive to most men, 60 mgm. of radium costing about \$4,200.00, and 100 mgm. costing about \$7,000.00. Therefore, such large amounts as 4 gm. cost \$280,000. Only large endowed institutions can possess these amounts. The technique of deep x-ray therapy and deep therapy by means of radium "bombs" will be discussed later.

Cutler feels prolonged radium treatment is much more desirable than the rapid longer doses. He states, "The weight of evidence for prolonged irradiation is incontestable." He points out, as did Regaud, that prolonging the time allows the radiation to get at the cancer cells when they are in mitosis or when they are most vulnerable; and, also the fact that prolonging the time permits the normal tissues to withstand much larger doses than is possible by short intense exposures.

Cutler's technique is to use 60 mgm. equally divided between the uterus and vagina. In order to administer 8000 mgm. hours his uterine applicator remains in place 80 hours and his colpostat 133 hours. He feels 80 mgm. is the largest that should be used. He uses 1 mm. platinum as a filter, with rubber to protect from secondary rays. They have at their disposal 4 Gm. radium for external irradiation and the technique is the same as that of Regaud, and will be described later.

(d) Mayo Clinic. There, the technique is comparatively simple. A 50 mgm. tube with a filter of .5 mm. of platinum and a secondary filter of rubber is first placed in the vagina for 14 hours two times a week. Then the tube is placed in the cervical canal for two occasions in a week, then in the lower part of the uterus, then in the upper part of the uterus. Results are given later.

3. X-Ray and Telecurie Therapy.

(a) Discussion. (The general history of x-ray has been considered in Section IIIB1.) It is generally realized that this form of irradiation is of vital importance in treating carcinoma

of the cervix. At present Healy states, "It would seem that all institutions which are endeavoring to carry out treatment of cancer of the cervix, or in fact any pelvic organ, should be properly equipped with facilities for deep x-ray therapy by means of a high voltage apparatus, since radium used only as a local application to the cervical canal is recognized as being insufficient. It fails to give the large number of advanced cases adequate radiation to outlying portions of the tumor growth. A radium pack element of sufficient size will of course do instead of x-ray, but it is not as economical."

All the techniques described above for the use of radium will get rid of the local lesion in the vast majority of cases. The failure to cure a patient is nearly always due to the growth continuing in the deeper parts of the pelvis and to metastatic deposits in lymph glands. This problem which faces the gynecologist is also common to all branches of radiotherapy. There are two possible causes of failure.

The first is that insufficient radiation is reaching the cancer tissue in the iliac glands and other structures deep in the pelvis. Second, it is possible that the deep deposits are actually more radio-resistant (see section IIIB1.)

X-rays alone are not as efficient on the local lesion, but there is considerable evidence that patients who have been treated by x-ray plus radium have benefited to a greater extent than those treated by radium alone. The statistics of survival rates bear this out. There are various methods of giving x-ray therapy in this disease, as to dosage, time of administration,

etc which will be considered. The controversy between deep x-ray and telecurie therapy has been discussed elsewhere.

(b) Techniques Employed.

1. Paris. Regaud follows the radium treatment with either the 4 Gm. radium bomb (more frequently) or x-ray in the following method. His first administration is given 12 to 21 days after the first radium. The voltage used is 180 to 200 KV and the current 4 to 5 milliamperes. The skin distance is 60 to 80 cm. The filter employed varies somewhat, but is between 1 and 2 mm. of copper. The skin is divided up into 8 fields of 250 sq. cm. each. Every field has 5 to 8 exposures split up in daily doses, one hour in the morning and one in the afternoon. The total period of treatment varies with the number of fields irradiated, but usually amounts to 25 days.

They use the telecurie method more frequently. They have 4 Gm. of radium which has been set aside for this treatment. The container, which is cup-shaped, has walls 6 mm. thick. The aperture is rectangular in shape and measures 150 sq. cm. The radium is applied at least 10 cm. from the skin and the filtration is equivalent to 1 cm. of platinum. The whole container, which is very heavy, is slung over the patient's bed on a sliding bridge. The skin surface is divided into 8 fields as for x-ray and sometimes a perineal field is added. The amount of radiation usually administered is slightly below the skin erythema dose, and this takes 10 hours for

each field. Thus the patient usually has a total of 80 hours irradiation. The daily dose lasts for three hours, and at the end of 8 days each field has been irradiated. Then a second series is started, and again one field is irradiated each day for three hours. Finally a third series of four hours per field is carried out. Treatment is therefore generally spread over 25 days. There is apparently very little general reaction, supposedly much less than with deep x-ray therapy, but Lacessagne mentions headaches, giddiness, nausea and vomiting and diarrhea may occur at the beginning, in which case the dose is modified, and will take a few extra days. The blood picture is supposed to be little modified at the end. During the whole treatment the patient is kept in bed. They have been sufficiently pleased with their results and at present have a new 8 Cm. "bomb" which they feel will further increase their cures. It will be seen in section IV, the increase in the number of cures when accessory deep therapy was instituted.

2. Memorial Hospital. Healy has used combined radiation since 1922. He remarks, "We have been pleased to observe that our constant insistence on the necessity of some form of external irradiation to take care of the entire pelvic field is now recognized and is apparently quite generally followed elsewhere."

There are still differences of opinion as to the plan of treatment of these two agents. In the majority of clinics treatment with radium precedes treatment with x-ray, and that was the plan followed at Memorial until 1931.

Healy was impressed by the high percentage, not only of advanced cases, but of extensively ulcerated and infected lesions coming for treatment in which the adjoining normal tissues were considerably involved in reactionary changes, due to the presence of an infected cancer. It seemed to him they should spend at least a short time in an effort to prepare the lesion for the application of radium. He has observed such lesions, in many cases, subside and almost disappear under x-ray alone, where palliation only had been planned. Thus he felt that hope to attain greater regression and possibly a higher curability rate, with less radiation complications, must lie in preliminary external radiation, with the use of vaginal antiseptic douches for a period of 10 days to two weeks preceding. He feels certain better results are obtained in this manner.

However, in favorable cases, he uses radium first, and the x-ray cycle is given as soon as feasible after the radium. They also deem it advisable to give a second x-ray cycle 8 to 12 weeks after the first radiation regardless of the stage of the cancer.

Since 1929 Healy has been using the following x-ray treatment generally, but sometimes 4 Gm. "bombs" are employed. More intensive treatment is his motive in an effort to treat parametrial metastases. The treatments are given daily or on alternate days. Under the multiple dosage plan the pelvis is divided into right and left halves and each into an anterior and posterior field. The two fields in one half of the pelvis

are treated one day, 200 "r" to each field at 70 cm., and the two fields in the other half the next day. This is done until each field has received 1000 "r"; the dosage for each exposure is then increased to 300 "r" and treatments are continued daily until 1500 "r" additional have been given to each of the four fields. It is estimated that under this plan the parametrial structures 10 cm. below the skin surface receive the equivalent of about $\frac{2}{3}$ the total skin dose or about 1600 "R".

Some say it is doubtful if 1600 "r" is sufficient, and yet reports of serious damage to the intestine are becoming more frequent as attempts are made to increase the depth dose to 2500 "r" or 3000 "r", even if given more slowly than the above.

There are numerous other methods of external therapy, but these are the two accepted as the most efficient in each type of treatment. Most of the others are minor variations from these.

4. Complications.

The effective treatment of cancer necessarily carries considerable risk to the patient. The risk is much less with irradiation than with operation but irradiation carries definite dangers. Heyman states that minor complications are present in about 10%. The serious responsibility and difficult problems in the use of radium are not generally appreciated. If the dose is too small, the distant cancer cells survive and the patient dies of recurrence. If the dosage is pushed to the point of causing devitalization of the outlying cancer

cells, there is danger of irradiation injury to the rectum, bladder, and ureters. With every patient that confronts the radio therapist he must think of the presence of infection, toxemia, anemia, diabetes, obesity, etc.; the danger of late bladder ulcers, vesical hemorrhage, rectal ulcers, stenosis of the bowel, and intestinal obstruction. Pyometra before and after radiation is also a problem. Rectal and vesical fistulae must likewise be considered.

Healy believes the external radiation before application of radium is an important factor in reduction of local infection and thus the prevention of a septicemia. In two weeks the lesion is generally greatly improved and the surrounding tissue in much better shape to receive radium.

The use of interstitial radium in advanced and infected cases is now recognized as unwise, because of the danger of necrosis and sloughing with the formation of fistulae, severe hemorrhage and death.

The bladder and rectal symptoms are important. The mild symptoms occur coincident with or immediately after completion of the treatment and subside in 10 to 14 days, and are well known, but the late bladder ulcers, which occur in about 2% of cases treated, come on a year or more after treatment when the patient may appear quite well otherwise. The chief symptoms are polyuria, dysuria, and vesical bleeding, and a cystoscopic examination reveals a lesion, usually ulcer, in the bladder base. These usually respond to persistent treatment in the form of bladder irrigations, instillation of

mild astringents and rest, and when cured, do not recur.

The late intestinal lesions are not so common, but consist of areas of localized ulceration in the small and large intestine, often associated with a rather severe blood loss from constant leakage of small quantities of blood so the patient becomes profoundly anemic and requires transfusion.

Sometimes the irradiation affect is shown by an intense inflammation involving all the walls of the upper rectum and lower sigmoid for a level of several inches, so the bowel in the affected areas is rigid, infiltrated, swollen, covered by fibrinoplastic exudate and resembles an acutely inflamed appendix. Such a lesion, if it subsides without perforation, tends to result in stenosis of the intestinal lumen and obstruction at a later date. These generally lead to operation for relief.

Then there are the milder forms of rectal stricture (Crossen reports 5 cases out of 371) which generally yield satisfactorily to dilation treatment. It emphasizes the importance of rectal examination in the check up, as well as paying attention to any rectal complaints.

There was one case of sloughing of the skin, in Crossen's series (771 cases), which was very extensive but went on to subsequent healing, and one case of first degree subcutaneous infiltration which remained stationary.

The general concensus of opinion is that the mortality from radiation of cancer is between 1.5% and 2%, which is due almost entirely to infection. When the temperature rises

during irradiation, the treatment must be promptly discontinued. An old adnexal infection may be lighted up by irradiation. Hemorrhage is an uncommon complication and radiation is generally continued. The importance of proper training before using radiation is stressed later.

5. General Treatment.

As in any other disease, general treatment is essential in preparation for radiation as well as proper medical treatment concomitant with radiation. Local cleanliness, nourishing food, sunshine and medical management are equally important. Afebrility means absence of infections, either local or systemic. Corroboration of infection is obtained by a high leukocyte count and a rapid sedimentation time of the red blood corpuscles. A culture of the predominant organism in the vagina is done by some and if streptococci are present treatment is delayed while antiseptic douches are used.

Radiation therapy is contraindicated in the presence of: (1) general emaciation, cachexia and toxemia due to absorption of waste products. Radiation almost invariably aggravates these states; (2) anemia with a red cell count below 3,000,000, a hemoglobin percentage below 50, and a leukocyte count below 3,000. Radiations may cause an increase in these conditions to a danger point; (3) impaired nitrogen metabolism. Radiation may produce a rapidly increasing N retention due to the liberation of proteins, especially in advanced cases. This may assume dangerous proportions in the presence of an already

impaired N metabolism; (4) invasion of the urinary or rectal tract. Radiations, especially radium, lead to a rapid destruction of cancerous tissues and subsequent formation of fistula; (5) the presence of infection. Local manipulations contribute to a spread or reactivation, especially when radium is used. Roentgen-rays, however, may be applied, but should be stopped if a rise in temperature ensues.

C. Miscellaneous.

There are numerous other points which could be included in the treatment of carcinoma of the cervix, but like the treatment of any disease, the field is flooded with methods which have been tried and are of no avail. Among these are the use of other radioactive heavy metals as bismuth; radiation of the pituitary in conjunction with local treatment; and the production of sterile gluteal abscesses, all of which have no permanent place.

There are other methods and various phases of the treatment of this disease which must be included however.

1. Combined methods.

It has been seen above that no one method can be used alone, and a combination of local radium, external radiation, and general care must be used.

There is one phase of combined treatment which merits mention, as it is seen in current literature. Chief among these are Cellhorn (1934) of St. Louis, and Curtis (1933). It is the use of combined intravaginal and intraabdominal radium.

The first attempts at this were made in Brussels in 1919. In 1921 intraabdominal radium was applied by other workers, among whom were Schwart, Richard, Douay, Fabre and Proust.

Space does not permit a detailed description of this procedure, but it will suffice to say, the abdomen is opened, the intestines packed away, and the pelvic cavity exposed to sight and touch. One hand is inserted into the vagina while the other is kept sterile for intraabdominal work. The extent of the lesion can thus be made out clearly. Then gold radon seeds are placed beneath the peritoneum in such a way as to form a complete ring around the cancerous area. They use about 4200 to 4500 mgm. hours of radium, half of which resides in the radon seeds. They generally use about 14 seeds, some of which are placed at the commoner lymph glands where metastases are found. Some close the abdomen and reopen later to remove the seeds. Others leave "leaders" of thread to them and remove them without reopening the abdomen.

Gellhorn is quite enthused about the procedure and feels it has a place in the future.

2. Treatment of Advanced Cases.

There are, of course, a fairly large number of patients coming to the physician too late to accomplish anything but palliation. These are the cases included in late stages of Group III and all of Group IV in the Clinical Classification. Of all the measures at the disposal of the physician for prolonging the life span of these women, high-voltage roentgen therapy is by far the most important. For effective treatment

an apparatus is needed which will deliver 200,000 volts.

In 80 per cent of these cases vaginal bleeding will stop, and in 30 per cent there will be complete relief of pelvic pain. With control of the local lesion there is generally a marked improvement in the general condition of the patient, and some are able to return to work. The relief is generally only temporary, however, and recourse to various other methods must be taken. In a group of 658 cases with inoperable lesions, (reported by Behrey in 1934), 305 or 45% remained symptom free for at least one year. Of 387 patients followed 5 years or longer, 38, or 9.8% remained well, two being well 12 years after beginning of treatment.

The antiseptic effect of high-voltage roentgen rays is well known. It is the most effectual and practical means of dealing with the infectious complications. The value of this has been seen previously.

The acute anemia from massive hemorrhage is best treated by tightly packing the crater and the vagina with sterile gauze and the application of a snug T binder. This is removed in 24 hours. The vagina and crater cleansed, and if bleeding recurs, the packing must be replaced. The blood loss should be compensated by venoclysis of glucose in normal saline and rest secured with opiates and hypnotics. Then a blood transfusion is indicated. Small transfusions and hematinics should be used for small quantities of blood loss.

Extension of the neoplasm into the parametrium often compresses the ureters and produces hydronephrosis which slowly

destroys the function of the kidneys. The patency can sometimes be restored by careful dilatation. If uremia is present nothing is attempted as this affords a painless and fairly rapid termination of the disease. Rectovaginal and vesicovaginal fistulae occur rarely if high voltage therapy alone is used. If present, the annoyance of a rectovaginal fistula can be greatly decreased by a properly planned diet and by the use of drugs which control the frequency and consistency of evacuations. If the vagina is cleansed with a soothing douche, after each movement, there need be little discomfort. Vesicovaginal fistulae are more distressing because of the continuously offensive odor and irritating effect of ammoniacal urine. This and phosphatic deposits on the skin can be prevented by keeping the urine faintly acid with sodium phosphate. If the skin becomes inflamed it should be cleansed frequently with boric acid solution and a mildly acid ointment should be applied.

Carcinoma may extend through lymphatics to the pelvic wall or to the vertebral column and there involve bone. This can be recognized by x-ray examination. Such bony metastases are usually radiosensitive and in most cases deep roentgen therapy not only relieves the pain but also retards the progress of the secondary lesion.

The excruciating pelvic pain seen in these patients is often due to involvement of the afferent sympathetic fibers. Paravertebral block by alcohol injections, into the posterior roots of the spinal nerves from the 10th thoracic to the 3rd

lumbar segments inclusive, is said to relieve this pain for 2 to 12 months. Cordotomy and excision of the superior hypogastric plexus (presacral nerve) have been employed with relief.

A high caloric diet is required, careful attention to the bowels to prevent either constipation or diarrhea. They should be encouraged to remain ambulatory and follow their normal interests as long as possible. A recumbent posture favors the development of decubitus sores and hypostatic pneumonia. Fresh air and sunlight promote a feeling of well-being and strengthen the resistive powers.

Even in absence of pain these patients are entirely comfortable. Nervousness and insomnia are frequent complaints and are common after narcotics have been withdrawn following the surgical relief of pain. In such situations, sedatives are almost indispensable. Amidopyrine, acetyl salicylic acid, or antipyrine will alloy pain in most instances, but opiates by mouth, by rectum or by hypodermic dose may be required, only after other methods have been tried unsuccessfully.

Section IV

Results and Conclusions

Throughout other portions of this paper results have of necessity been given, but an attempt will be made to organize them and draw conclusions. It is evident that one must depend upon end results as indicated by the total salvage of all cases in order to eliminate the personal equation and obtain a proper estimate of the real value of any method of treatment. The difficulties in attempting comparisons of various methods were given in Sections II and III.

Perhaps the best statistical enquiry ever attempted in regard to this subject, was that undertaken by Dr. Janet Lane - Claypon, for the Ministry of Health of England in 1927. She included all other reports then available. She reported 6661 cases that were operated by vaginal or abdominal hysterectomy, and of these 2222 were alive at the end of 5 years, making a survival rate of 34.1%. Of 1117 technically operable cases treated by radiation alone, 400 were alive at the end of 5 years, or 35.8%. In the same report she compared the survival rate of all cases seen. She estimated in clinics which adopted excisional methods 18.3% all patients presenting themselves were alive at the end of 5 years, whereas, in those clinics where radiotherapy alone was practiced 22% survived 5 years or more.

Heyman of Stockholm in another report states 3659 cases treated by hysterectomy 35.6%, and 960 early cases treated by radiotherapy 54.9%, lived over 5 years. The best figures for

operation in the individual clinics in that of Weibel, who shows a survival rate of 47.8%, while the best figures for radiotherapy are 50%. A statistical survey, therefore, suggests there is very little difference between the two methods of treatment in early cases, but the immediate mortality of surgery has been seen to be about 17% or more while that of radio therapy is around 1.5%.

The advantages of each type of treatment and the indications have been previously considered.

In choice of treatment it is well to recall the words of Victor Bonney who reports an absolute cure of 24.4% with a modified Wertheim method, "That which is beyond the scope of radium includes certain cases not beyond the scope of surgery, and that which is beyond the scope of surgery includes certain cases not beyond the scope of radium." This was stated several years ago, and the trend of opinion now has been seen to be toward surgery only in Group I lesions, and then many doubt if it should be used then. It is estimated by various authorities, as has been seen previously, that this group only includes about 2% of the total cases.

It is not the place of the general practitioner to feel qualified to do the radical operations with success. Only after appropriate post-graduate and personal instruction from a master in this field of surgery, should he attempt to take the responsibility of such an operation. The same holds for radium and roentgen therapy, which requires a thorough theoretical and practical knowledge for its operator to obtain the

desired result.

Healy's impression of the subject, (1934) is, "One can see that it becomes difficult if not impossible to compare methods of treatment as different as surgery and radiation when one must depend on statistics from different clinics. The quality and variety of cases seen in the individual clinics varies considerably, the detail of the operation will vary with each operator, the methods of carrying out radiation therapy vary almost more than surgical procedures, and here again the personal equation of the physician in charge becomes important. For one reason or another it would seem that radiation therapy in carcinoma of the cervix is gradually supplanting surgery."

Of course, some of the same objections to surgery apply to radiotherapy. Radiation statistics come from radium institutes which have the best trained therapists for radiation therapy. It must be conceded, therefore, that the average results are somewhat lower than those found in literature. Also radiation statistics are subject to almost the same criticism as surgical statistics.

Radiotherapy Results.

Paris (Regeud).

Lacassagne (1932) reported in detail on the results obtained at the Radium Institute, and it shows several important facts. The results improved steadily from 1919 to 1926 in five-year cures, and this he attributes to the regular progress achieved in radio therapeutic technique, and he feels further progress is bound to come.

From the point of view of technique, the eight years under review falls into three distinct periods. The first, which comprises the years 1919 and 1920, "just after the department was opened, was a period of initiation and testing of the personnel". Cervical cancers were irradiated with material that was not properly adapted to its purpose, and by diverse methods which subsequent experience has led them to regard as defective. The results showed 10 to 17% only of cures. In 1921 the staff instituted their technique of introducing radium into the uterine cavity, and have not appreciably modified it since; it is still given systematically in each case, as seen previously. Nearly all the cases treated 1921 to 1923 received this treatment alone. Though inadequate, its merits are apparent in the increase in the rate of cure, first to 25% and then to 30%.

The staff then became convinced to the necessity of reinforcing the treatment by external irradiation, exciting as uniform an effect as possible on the whole pelvic cavity. From 1924 onwards this combined treatment has been used, especially in all cases which showed parametrial involvement. The method has been described. This resulted in another improvement in 5 year cures to 35 and 36%.

The period of 8 years thus was divided into two 4-year periods, each comprising an approximately equal number of cases. Lacassagne considered the comparative results for the two periods, and analyzed each separately, according to the various stages of the disease. In stage I the total number of cases

was 52. In 30 cases treated during the first period 10 cures were obtained (33%); but of 22 patients treated during the second period 19 were still well after five years (86%). The number of cases in stage II was 200; the 104 treated in the first period gave 26% cures; the 96 treated in the second period gave 42%. In stage III cases, there was still a more striking proof of progress. Whereas only 8% of 111 patients were cured in the first period, the number cured out of 152 treated between 1923 and 1926 was 46 (30%). In stage IV, on the other hand, the growths are practically incurable, and there was no progress made. These are the results of radiotherapy in one of the best clinics five years ago, and it is reasonable to expect that patients being treated now will show a proportionate increase.

Stockholm (Heyman at Radiumhemmet Institute).

Owing to a number of local conditions, mainly government control, the Swedish Cancer material offers more accurate statistics on results obtained than any other country. The Swedish authorities have long insisted on the necessity of completeness of figures in enumerating what have been termed "absolute cures", or the number of patients alive and free from symptoms five years after treatment, compared to the total number of patients who applied for treatment. In other words, there is no elimination of hopeless or incurable patients.

Records show the total number of patients applying for treatment in the 13 years preceding January, 1927 was 1237.

Of these 259 are alive and well, an absolute cure of 20%. The 10 year absolute cure was 16%, but all patients who died of intercurrent disease were reckoned as having died of cancer. The 5 year cures are considered to be more desirable because the normal expectation of life at 45 to 55 years of age is relatively low. Of those who did not survive 5 years, some 60% were greatly improved and were able to return to their occupations for a time. The number of patients refusing treatment was about 6.5% of all applicants. If statistics are computed on the basis of those treated, the percentage rises from 20 to 22%. Of 1157 treated, some 73% were inoperable. Of these "inoperable" and "borderline" cases the 5 year cure was 16%, with the operable cases being 41%. Only during the last few years has additional x-ray or teluradium exposures been given, and they state it is yet too early to draw conclusions. Marie Curie Hospital (London). (From the Eleventh Annual Report of the British Cancer Commission.)

They use the Stockholm technique of "split dosage", giving a total of 7410 mgm. hrs. in 3 doses, over a period of five weeks.

They report a steady increase in the ratio of early cases admitted for treatment, the percentage of degrees I and II increased from 17% in 1926 to 35.4% in 1933. The report includes the years 1925 to 1928.

	Total number treated	--	215	
	Living five years	--	72 (33.48%)	
<u>Stage</u>	<u>Number treated</u>		<u>Living</u>	<u>Per cent.</u>
I	11		9	81.8
II	36		21	58.3
III	124		38	30.6
IV	44		4	9.0

Munich (Doderlein).

(Years of treatment 1924-1926)

<u>Groups</u>	<u>Number treated</u>	<u>5-year survival</u>	<u>Per cent</u>
I	99	49	49.4
II	91	21	23.1
III	129	23	17.9
IV	85	4	4.9
Totals	404	97	23.8

Schmitz (Chicago).

For the period 1914-1919, the percentages of 5-year good end-results in the four groups were as follows: Group one, 100; group two, 43.75; group three, 9.21; group four, 0; for the period 1920-1921, 66.67, 46.75, 7.69, and 0, respectively; for the period 1922-1923, 77.78, 36.84, 18.65, and 0; for the period 1924-1929, 91.3, 52.78, 30.0 and 6.04. The grand total for the whole period 1914-1929 was 84.77, 47.62, 19.16, and 3.24 in the four groups, respectively, with a final total of 22.26 in all combined.

Ward (Womans' Hospital, New York).

His total treated was 343, 85 of which were alive 5 years after treatment, or 24.8%.

As has been mentioned before the cure rate of these clinics is higher than that obtained the country over.

Conclusions

1. The most important item in prophylaxis is proper treatment of lacerated cervixes which have become chronically infected, as carcinoma is believed to occur very seldom, if at all, in a normal cervix.

2. Periodic examination of all women, particularly those who have borne several children, for the detection of malignancy, because the early symptoms are all objective. This would include a Schillen test, and biopsy for those negative to the Lugol's solution.

3. Clinical classification is much more important in prognosis and response to treatment, than histopathologic classification, but the latter has its place in the decision to use surgery in some cases.

4. The League of Nations Classification should be used universally, in order to obtain uniform records in the study of incidence and the response to treatment by different methods.

5. Excisional surgery has apparently reached the peak of perfection, and can advance no further. It has an immediate mortality of about 17% or higher, depending on the operative skill of the surgeon. The chief argument in its favor is the ablation of cancerous deposits in the glands, and this alone can be its justification. Newer radio therapy methods are striking at this difficulty and bid well to show marked advancement in the future.

6. Radiotherapy is considered the method of choice at present, in all but the very earliest case, and many doubt if surgery should be used then. The immediate mortality in radiotherapy is between 1% and 2%, and complications, mostly mild in character, about 5 to 10%, and these will probably be reduced markedly in the next few years as advances in technique are made. The statistics of survival rate in the early cases are

in no way inferior to those of surgery. The patients are not deterred from seeking early advice by the prospect of a severe operation. About 12 to 16% of patients beyond all surgical aid are restored to health and survive more than five years. As a palliative measure in advanced cases no other measure at present is known to be so beneficial. There are various methods of irradiation in use, but the essential thing seems to be adequate dosage over the proper length of time, applied by one who has both theoretical and practical knowledge of the subject. All the leading clinics get approximately the same 5 year cure results. The average is around 25 to 28%. Combined radiation is recognized as essential. Radium for the local growth and external therapy for parametrial and glandular involvement. External radiation promises more in the future.

7. Education of the public in regard to the necessity of treatment of "pre-cancerous" lesions is essential in the prophylaxis, as is the importance of periodical examination. About 67% of the cases coming to physicians are classes as inoperable. The opinion that cancer is always incurable and the public dread of "cancer" should be dispelled.

8. Establishment of well-equipped cancer clinics with an adequately trained personnel within reach of all, will be a vital step in the control of cancer.

Section V

Future Problems

The improved statistics published by the various clinics, especially those of Regaud, indicating as they do a better plan of external irradiation of the pelvis, seems to justify the leading radiologists in their belief that they are on the right track. Internal radiation, and more so at present, external radiation properly carried out still offers the best chance of cure in the patient suffering from cancer of the cervix.

Healy (1933) states, "I believe at the present time that external radiation with x-ray or strong radium packs offers the most encouragement. But the task is difficult and not easily surmounted. Glandular metastases do not seem to be as susceptible as the primary lesion, nor are they as accessible to treatment. The rays have to pass through the abdominal organs which are more or less damaged, and the limit of radiation dose is the tolerance of these normal structures. The tolerance is not always sufficient to permit enough effective radiation into the cancer bearing tissues in the parametrium and the retroperitoneal lymphatics along the spine. It is necessary to increase the radiation to the parametrium, even in the face of the complications, if 5 year cure of early cases is to be increased.

Lacassagne (1932) states, "There is every ground for thinking that the cure rate will be still further improved, though possibly not at such rapidity." He feels that another

problem at present is the control of infection. "The immediate mortality from gynecological radium therapy is entirely due to infection and hardly amounts to 2%. In a greater proportion the irradiation sets on foot infective processes which interfere with treatment, and consequently the cure. If we could find an adequate antidote for the streptococcus, one of its most useful effects would be to increase considerably the proportion of cures in uterine cancer."

The chief problem seems to be the fact that too many patients come in for the first time suffering from stage IV lesions. The efforts being made in all countries, especially on the continent, to bring cancer under treatment earlier must inevitably reduce the number of these unfortunate women. England, Sweden, and France seem to be the most active in these campaigns. The American Society for the Prevention of Cancer has a very difficult problem because of the huge area it includes. In the Eastern states one can see bill boards urging patients to be periodically examined, and explaining that cancer is curable in the early stages. The most active work can be done by general practitioners. They should interest themselves in the subject and if they feel they are incapable, they should see that the patient gets to a cancer clinic for confirmation of the diagnosis, and treatment if needed. The physician should continue to carefully observe the course of any treatments given, make definite appointments for examination and check-up upon the finish of any treatment.

Improvement in the end results of cancer are seen all over the world where special groups of individuals have been

permitted to organize and devote themselves to the intensive study and treatment of this disease.

Opportunities for advancement along this line is far from being exhausted. Greenough states, "Each of the different methods of treatment which are recognized today as efficient in the treatment of cancer require a long period of study and apprenticeship before the technique of the application of treatment, whether it be surgery, x-rays or radium, can be successfully acquired. Because of this it will be necessary for several physicians, each qualified in his own line of work to work together in close cooperation and intimate consultation, to treat this protean disease. Such a group can function efficiently only in a special cancer clinic."

Donaldson (1933) emphasized again the fact that there should be a large number of the centers so the patient would not have to go far in order to get a thorough examination. He felt that every county hospital should have a diagnostic center attached to it. He stated, "It might be possible at a cancer center to train men so that they could single-handed examine a patient by all the most modern methods in order to exclude malignant disease." It would be rather difficult to get a thorough training in all the branches because it would take a life time. Thus it is better to have a group of men. Of course, the financial backing is the deciding factor and one must make the best of the facilities and training he has at his disposal in each locality.

Bloodgood has remarked, "One of the essentials in bettering the results of cervical carcinoma is a large number of trained radiologists, and that they should have a clinical surgical training in addition. With such preliminary experience on the part of the radiologist, with attention by the surgeon and family physician to early diagnosis, and their close cooperation with the pathologist, we may hope to bring the unfortunate carcinoma patient under treatment at a time which will, or should, enable us to save 80% at least."

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