CARCINOMA OF THE CERVIX

Trends in Treatment

ROBERT A. HAYS, M.D. and U. V. PORTMANN, M.D.
Department of Therapeutic Radiology

DESPITE numerous technical and clinical advances in the methods of treatment of carcinoma of the cervix, 65 to 75 per cent of patients with this disease die within 5 years. There are many factors responsible for this alarming death rate, the most common of which is the failure of patients to seek medical advice early enough. In Miller's[1] series there was a 7 months' delay from the onset of symptoms before medical attention was sought. Another factor is that physicians frequently minimize the importance of symptoms and do not recognize the signs of cancer of the uterus.

In considering the treatment of uterine cervical cancer, it is customary to classify cases according to the League of Nations Stages.

Stage I

The carcinoma is strictly confined to the cervix.

Stage II

Parametrium—the carcinoma infiltrates the parametrium on one or both sides but has not invaded the pelvic wall.

Vagina—the carcinoma infiltrates the vagina but does not involve its lower third.

Corpus—endocervical carcinoma which has spread to the corpus.

Stage III

Parametrium—the carcinomatous infiltration of the parametrium on one or both sides has invaded the pelvic wall. On rectal examination no cancer-free space is found between the tumor and pelvic wall.

Vagina—the carcinoma involves the lower third of the vagina. Isolated carcinomatous metastases are palpable on the pelvic wall (irrespective of the extent of the primary cervical growth).

Stage IV

Bladder—the carcinoma involves the bladder as determined by the presence of a vesicovaginal fistula.

Rectum—the carcinoma involves the rectum.

Distant spread—the carcinoma has spread outside the true pelvis (below the vaginal inlet, above pelvic brim, distant metastases).

This clinical classification has considerably more bearing on the prognosis and therapeutic regimen than the pathologic grading of the tumor.

Eighty per cent[2] of patients reporting will have extension beyond the cervix when first examined. The number of patients surviving 5 years or more is proportional to the anatomic extent of the lesion. The general average of 5 year survivals is approximately 80 per cent in Stage I; 52 per cent in Stage II; 23 per cent in Stage III, and 3 per cent in Stage IV.[3]

In studying preinvasive carcinoma of the cervix, Pund et al[4] believe that most carcinomas have been present for a period of 2 to 6 years before causing symptoms. They base this on the fact that the average age of patients with preinvasive carcinoma is 36.6 years and for those with grossly detectable cancer 44.2 years.

General Consideration of Treatment

The treatment of carcinoma of the cervix with radium was popularized in the United States in 1912 by Kelly and Burnam.[5] Previously the method of treatment had been principally surgical. Wertheim and Bonney,[6] in Europe, had perfected their operative technic for selected cases and were obtaining a fair number of cures. However, they had a large operative mortality (12 to 20 per cent), and there was a long period of convalescence. In addition, the operation was technically difficult.

After its introduction, the use of radium became so popular that it soon replaced surgery. The reasons are obvious; there was ease of application, low primary mortality and minimal morbidity. However, after a period of experimentation, it was found that, in many cases apparently cured with radium, the carcinoma recurred in a year or more with parametrial involvement.

In the early 1930s much work was done on radium dosage. Arneson[7] studied the dosage delivered by radium when applied by various methods. He concluded that a tandem in the cervix and uterus, plus colpostats in the lateral fornices, gave the best distribution without over-irradiating normal tissues. He found that the dosage delivered decreased greatly toward the lateral wall of the pelvis. It was also observed that it would be impossible to bring the dosage up to a cancerocidal level in the parametrium by means of radium alone.

Since the local lesion in the cervix can be controlled readily by radium, it is the involvement of the parametria and pelvic lymph nodes which determines the outcome. Fricke[8] points out that the nodes are located several centimeters from the cervix. The nodes first involved are the primary nodes: the hypogastric, the obturator nodes at the bifurcation of the common iliac vessels, the external iliac chain, and the ureteral nodes. The secondary nodes, which are usually involved later, are those in relation to the common iliac vessels, the middle and lateral sacrals, and the aortic chain.[9]

Because of the limitations of radium dosage, external roentgen therapy was used to supplement the radiation, particularly to the parametria. A constant effort has been made, since this time, to administer as large a dose of roentgen rays and radium to the tumor and its extentions as is feasible and still preserve the normal uninvaded surrounding structures.

It was determined, from experience, that squamous cell carcinoma could be controlled by 7000 to 10,000 r. The tolerance of the other normal tissues in the area must be considered in any plan of radiation therapy. The limit of tolerance of the bladder and rectum must be below 10,000 r and any amount over 7000 r to the femora endangers their vitality. The therapist must consider all of these factors in his estimation of dosage and its methods of application for each individual case.

Radiation Therapy

We believe that, wherever possible, treatment should be begun with preliminary external roentgen therapy followed by radium therapy. Roentgen therapy given first has five advantages:[3] (1) Neoplastic cells which may be disseminated by manipulation are devitalized; (2) lymphatics are partially sealed; (3) ever present local infection is diminished; (4) anatomic relationships, which are distorted by the cancer, are re-established, and (5) there is an increase of 5 to 10 per cent in the 5 year survival rate when roentgen therapy precedes radium application, particularly in advanced cases.

This initial roentgen therapy is given through direct portals, one anterior and one posterior. In most cases we attempt to give 1000 r to the parametria and cervix. Larger doses may cause atresia of the vagina or cervical canal, which complicates the application of radium.

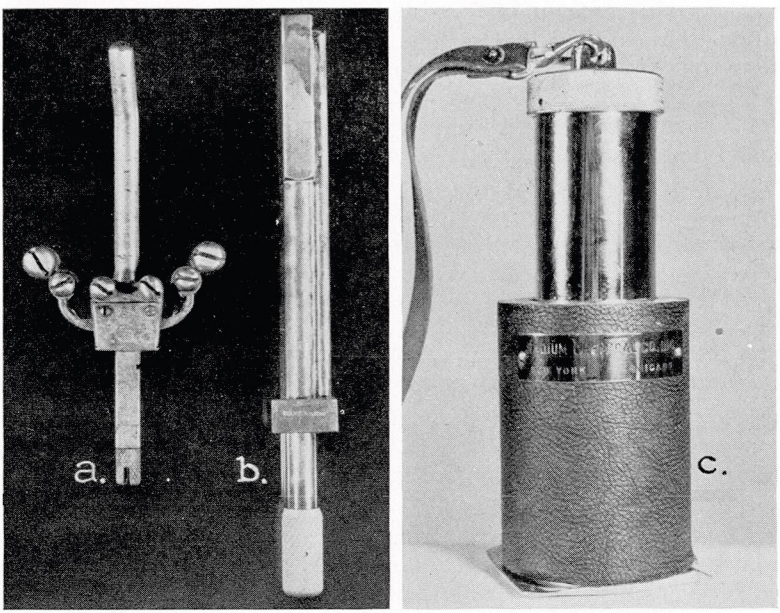

Fig. 1. (a) Ernst applicator in opened position. (b) Handle used for inserting and opening applicator. (c) Carrier for storing and transporting applicator. Personnel are protected by lead collar about carrier.

Following this preliminary roentgen therapy, patients are immediately hospitalized and radium is applied. For this purpose we have found the applicator designed by Ernst[10] of St. Louis to be extremely useful in many cases (fig. 1). It consists of an intra-uterine section containing three 10 mg. sources of radium, and expanding side arms for extension into the lateral fornices. Each side arm contains three 10 mg. radium sources. The total filtration of each is equivalent to 1.0 mm. of platinum. The applicator is inserted closed and the side arms are expanded after insertion. This not only delivers the radium laterally as far as possible, but it also serves to hold the applicator in position. A gauze roll impregnated with barium sulfate suspension is used to pack the bladder and rectum as far from the radiation sources as possible. Offensive odors are also minimized by use of the barium which also acts as an astringent. Anterior-posterior and lateral roentgenograms are made immediately following the insertion to check on the location of the sources. This procedure makes it possible to adjust the applicator, if necessary, before too much time has elapsed.

The advantages of this applicator are many: it is quickly and easily positioned and removed, thereby reducing the exposure of the therapist; the relative positions of the several radium sources remain constant and can be duplicated; the spacing of the radium tends to give a more adequate and homogeneous distribution of the radiation; the dosage to the bladder and rectum is minimal because of 2 mm. of lead incorporated in the ends of the vaginal sources and by the fact that the sources do not tend to slip.

The applicator is left in place for 48 hours and a second 48 hour application is made in 7 days. This fractionation permits giving a much larger dose than can be given with safety at one sitting. Using this method, 8640 mg. hours are administered which deliver 8500 gamma r to Point A; 3000 gamma r to Point B (fig. 2). These are the optimum doses advocated by Tod.[11]

Occasionally it is impossible to insert the complete applicator because of anatomic distortion of the structures. Under such circumstances one or more of the sources may be removed from either the uterine stem or from the vaginal portion of the applicator.

In cases that cannot be treated with the Ernst applicator, or in those cases which present unusual problems, some modification of the Manchester method may be employed (fig. 3). This technic was popularized by Tod and Meredith.[12] It consists of an intra-uterine tandem of radium sources and, in addition, 2 vaginal ovoids which are placed as far laterally into the fornices as possible, and held apart by a spacer. From the anatomic shape of the paracervical and parametrial tissues they planned the arrangement of the radium sources to give isodose curves which produced a cancerocidal dose at Point A. The radium is divided into units of 5 mg., 6.66 mg. and 10 mg. In the intrauterine tandem they place the following number of units, 2, 2, 1 with the single unit at the cervix. The ovoids for the fornices are of 3 sizes, large, medium and small, and contain 5, 4 or 3 units respectively.

Dosage by means of this system is calculated in gamma r and depends on the size of the unit employed, i. e. whether 5 mg., 6.66 mg. or 10 mg. Whether

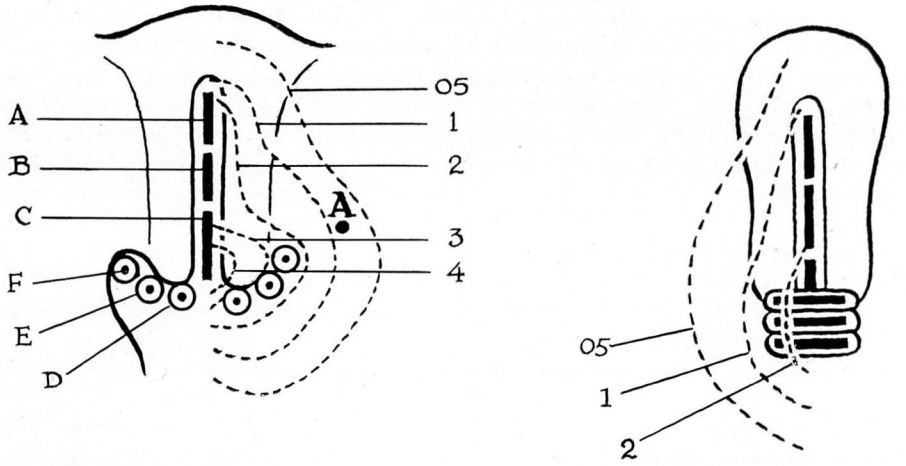

Fig. 2. Isodose curves in gamma r per mg. hour with fully loaded Ernst applicator.

one uses a small ovoid or a large one does not appreciably affect the dosage, provided the largest that can be accommodated is employed. With 5 mg. units 1000 gamma r will be delivered at Point A in 24 hrs.; 1333 r with 6.66 mg. sources and 2000 gamma r with 10 mg. sources. In this country Harris and Silverstone[13] and Hunt[14] have used a modification of this method with excellent results.

In addition to the methods of intracavitary radium therapy described, there are variations known as the Paris and Stockholm technics. The Manchester method is a modification of the Paris technic. The Paris method differs from the Stockholm technic in that it is a more or less continuous application of radium, and the vaginal and intra-uterine applications are not administered simultaneously but consecutively. With the Stockholm method 3 large doses are administered at weekly or biweekly intervals and the sources are more heavily filtered with lead than in the Paris technic.

Because of the failure of centrally placed radium to give a lethal tumor dose at the lateral pelvic wall, Pitts and Waterman[15,16] in 1926 initiated interstitial radium therapy with long needles for cancer of the cervix. Their technic consisted of inserting a 20 mg. radium tube into the cervical and uterine canal; 2 needles of 3 mg. content are inserted into each lateral fornix and 4 to 6 needles of 2 mg. radium content into each anterior and posterior fornix. The needles are left in place for 168 hours.

Corscaden et al[17] have devised a somewhat different approach to the method of parametrial radium needle implantation. Their technic consists of an intra-uterine tandem plus a stockade of 8 radium needles containing 2 mg. each inserted into the cervix. On each side, 1½ cm. lateral to the stockade, 2 needles of the same strength as the cervical needles are inserted. One and one-half cm. lateral to those needles, or 4.5 cm. from the cervical canal, 5 needles 6 cm. long and containing 4.8 mg. of radium are inserted against the

lateral pelvic wall. All sources are left in place for 120 hours. After operation, stereoscopic roentgenograms of the pelvis are made and by means of the precision stereoscope the dosage in gamma r calculated. With this method mentioned, 11,000 gamma r are delivered to the cervix, 14,400 to the paracervical region, and 10,000 gamma r to the lateral pelvic wall. This indicates that the dosage throughout the entire potentially diseased tissue is homogenous, balanced and adequate. The authors have used it in Stage III lesions and are encouraged by the immediate beneficial results.

Radioactive cobalt 60 needles are being used instead of radium needles and seem to offer certain advantages. They are thinner and cause less trauma than the conventional needles. The gamma radiation is more homogeneous than that from radium.

Roentgen Therapy

Because the intensity of radiation from radium sources obeys the inverse square law, there is a rapid diminution in the parametria laterally. It was recognized early that those cases which were not controlled by radium were ones in which the disease had spread beyond the cervix. Unfortunately, this was true in 80 per cent. As can be seen by the technics described there is a decrease to 3000 gamma r at the lateral pelvic wall. This amount is insufficient to control cancer.

In order to build up the dosage in the lateral portion of the parametria, interstitial radium needles or roentgen therapy are used. We believe that all carcinomas of the cervix should receive roentgen therapy in addition to radium, except in early Stage I lesions. The roentgen therapy should be started before radium insertion, as previously stated. Immediately after the radium treatment another course of roentgen therapy is prescribed. This is given through split anterior and posterior 15 by 20 cm. fields with a strip of lead 5 cm. wide in the center of the fields dividing them in two. A depth dose of 3000 to 3500 r is given to the parametria.

The reason for the split field is to protect the cervix, rectum, and bladder from further radiation, which in addition to the dosage from radium, might exceed the tissue tolerance of these structures. Lateral pelvic fields are not employed because we do not believe they add significantly to the dose, and fractures of the femoral neck may result from over-irradiation. Perineal fields are not advocated because severe skin reactions are produced and there is little increase in the depth dose.

Transvaginal administration of roentgen rays has come into popular usage in the last 10 years due to the efforts of Merritt,[18] Erskine,[19] Wasson,[20] and Sante[21]. This is accomplished by directing the rays through a cone inserted in the vagina. This type of therapy offers the theoretical advantages of a uniform field, adequate dosage, and directional control for selected cases.

A 3 cm. cone is about the largest which can be inserted into the vagina without excessive discomfort, and 30 cm. is the shortest focal skin distance that is practicable. Every effort should be made to divert the beam away from the

hollow of the sacrum and from the rectum. In some patients it may be possible to use a small cone and angle the beam into the right and left parametria. Nolan and Stanbro[22] believe that 3 vaginal fields of application offer the best distribution to the cervix and portions of the parametria. They advocate administering 5000 r to each field in increments of 300 to 500 r daily.

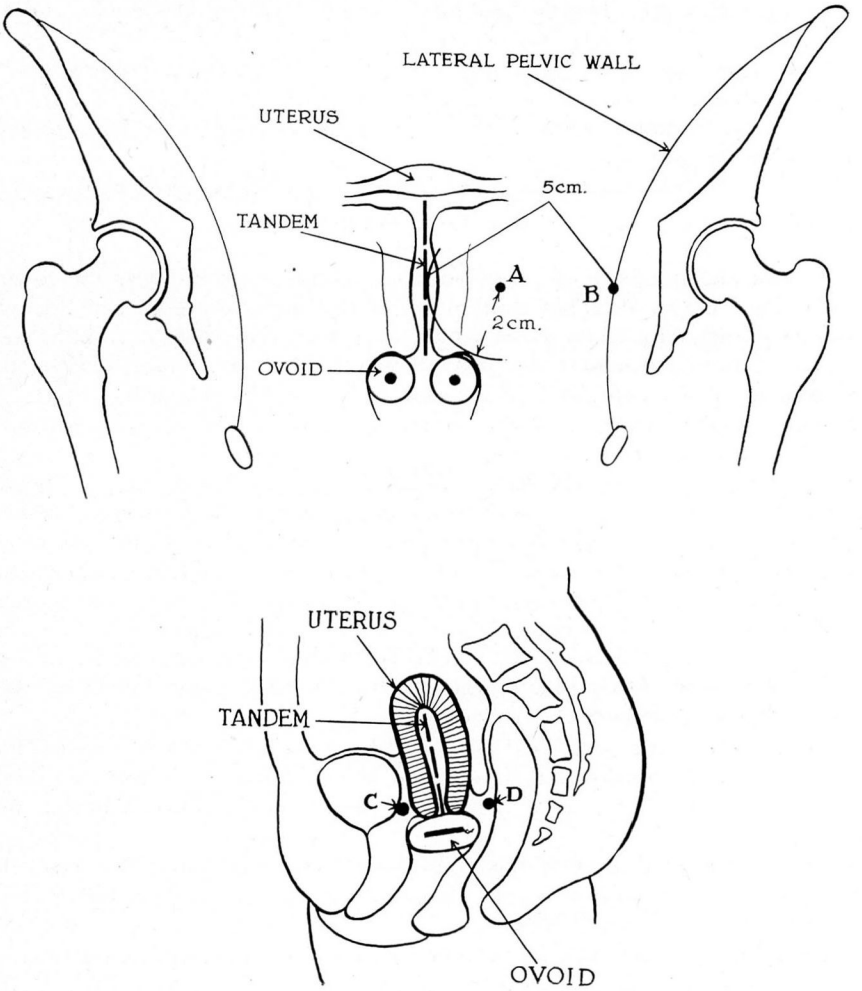

Fig. 3. Diagram of pelvis illustrating position of intra-uterine tandem and vaginal ovoids employed in Manchester system. Point A is located in paracervical triangle where uterine artery crosses ureter. This point is 2 cm. lateral to central axis of uterus and 2 cm. above lateral fornix of vagina. Point B, located in lateral parametrium 5 cm. from midline, is location of principle lymph nodes involved in carcinomas of cervix. Points C and D are bladder and rectal wall, respectively.

In some clinics this type of therapy has replaced radium, particularly for early lesions. External roentgen therapy can be used to supplement the parametrial dosage. It is particularly adaptable to carcinoma of the cervical stump and to patients who have had previous radium therapy with recurrences.

Surgical Treatment

While radiation therapy remains the treatment of choice for most invasive carcinomas of the cervix, there has been revival of interest in the surgical approach in Stage I and early Stage II cases. Since 1939 Meigs[23] has performed the Wertheim type of operation plus pelvic lymphadenectomy in these early cases. He believes that radiation therapy has reached a plateau and that something further must be done to improve results. From his observations at operation he believes that the pelvic nodes constitute the obstruction to the cure of some cases of carcinoma of the cervix.[23] He found metastases in 18 per cent of nodes in cases considered clinically to be Stage I, and 28 per cent in Stage II. Both Meigs[23] and Taussig[24] doubt the ability of radiation therapy to sterilize squamous cell carcinoma in lymph nodes. They cite the failure of roentgen therapy to control metastases in peripheral nodes, such as metastases in cervical nodes from carcinoma of the tongue. Taussig[24] advocated pelvic lymphadenectomy in Stage II cases either before or after radiation therapy.

Bonney operated on 63 per cent of the patients presenting themselves and had an operative mortality of 14 per cent. The over-all 5 year survival rate was 41 per cent. Read,[25] on the other hand, operates on only 14 per cent of his patients. Meigs recommends that the patient be under 50 years of age and thin. The tumor may invade the entire cervix and extend not more than 1 cm. into the vaginal wall. The cervix must be movable.

Results of Treatments

The results of treatment are based on the number of patients living and well at the end of 5 years. A large series of statistics has been compiled by Swanberg.[26] He reported on 1796 cases from 1933 to 1938, treated by several different radiation technics. The findings are listed in the Table.

	Stage I	Stage II	Stage III	Stage IV	Total
Number of patients	208	550	738	300	1796
Relative 5 year cure rate .	56.2	40.7	26.4	5.7	32.2

Meredith[27] using the Manchester technic of irradiation, has been improving his results constantly by giving larger doses with radium in Stages I and II and by adding roentgen therapy in Stages III and IV. He averages between 8000 and 9500 r at Point A. He believes that higher doses do not improve the results. Tod,[11] using these higher doses, reports a 3 year survival rate of 83 per cent in Stage I, 57 per cent in Stage II and 38 per cent in Stage III.

Meigs,[23] by carefully selecting his cases for radical surgery, had a 3 year survival rate of 77.7 per cent. Due to his strict rules for selection, it is possible that his 5 year survival rate will not differ greatly from his 3 year rate.

Arneson[28] compared the results of surgical and radiation therapy for carcinoma of the cervix in two large series of cases treated in different clinics. Bonney's surgically treated patients were compared with those given radiation therapy by Pitts and Waterman. Bonney treated 63 per cent of the patients presenting themselves and Pitts and Waterman treated 76 per cent in Schmitz Stages, I, II and III. The 5 year survival rate in Bonney's cases was 40 per cent and in Pitts and Waterman's, 76 per cent.

The controversy of surgery versus radiation in the treatment of Stage I and II cases revolves about the inability of radiation to control carcinoma in lymph nodes. Taussig[24] compared results among 70 iliac lymphadenectomies and 118 Stage II patients treated by irradiation alone. While 38.6 per cent of patients with node dissection survived 5 years, the rate was 22.9 per cent for radiation. Morton[29] noted that there was 39.3 per cent involvement of nodes in cases operated upon with no irradiation and only 11.4 per cent in postirradiation cases. Obviously no positive conclusions can be drawn as yet from these figures.

Conclusions

Radiation therapy by the combined use of radium and roentgen rays is still the preferred method of treatment in the majority of cases of carcinoma of the cervix. The trend is toward larger fractionated doses of radium so that undesirable reactions are minimized.

Palliation of advanced cancers may be afforded by the judicious use of roentgen therapy. Radium is contraindicated in patients with severe anemia and cachexia.

Radiation in the form of interstitial parametrial needles appears to offer an excellent method of obtaining satisfactory dosage throughout the involved tissues.

A few expert surgeons have demonstrated that operation is satisfactory in early cases. It would appear that irradiation followed in 2 to 3 months by iliac lymphadenectomy offers, in suitable cases, a concrete means of improving our results and curing patients with involvement of lymph nodes.

References

1. Miller, N. F.: Consideration of certain factors pertaining to control of carcinoma of cervix. Am. J. Obst. and Gynec. **46**:625 (Nov.) 1943.
2. Meigs, J. V., Parsons, L. and Nathanson, I. T.: Retroperitoneal lymph node dissection in cancer of cervix. Am. J. Obst. and Gynec. **57**:1087 (June) 1949.
3. Kimbrough, R. A. and Muckle, C. W.: Treatment of carcinoma of cervix. Am. J. Obst. and Gynec. **56**:687 (Oct.) 1948.
4. Pund, E. R., Nettles, J. B., Caldwell, J. D. and Niebings, H. E.: Preinvasive and invasive carcinoma of cervix uteri: pathogenesis detection, differential diagnosis, and pathologic basis for management. Am. J. Obst. and Gynec. **55**:831 (May) 1948.
5. Burnam, C. F.: Early experiences with radium. Am. J. Roentgenol. **36**:437 (Oct.) 1936.
6. Bonney, V.: Results in 500 cases of Wertheim's operation for cancer of cervix. J. Obst. and Gynaec. Brit. Emp. **48**:421 (Aug.) 1941.
7. Arneson, A. M.: Distribution of radiation within average female pelvis for different methods of applying radium to cervix. Radiology **27**:1 (July) 1936.

8. Fricke, R. E.: Selection of therapy for carcinoma of cervix. Ann. West. Med. and Surg. 3:410 (Dec.) 1949.
9. Nathanson, I. T.: Cited by Fricke.[8]
10. Ernst, E. C.: Probable trends in irradiation treatment of carcinoma of cervix uteri with improved expanding type of radium applicator. Radiology **52**:46 (Jan.) 1949.
11. Tod, M. C.: Optimum dosage in treatment of cancer of cervix by radiation. Acta radiol. **28**:564, 1947.
12. Tod, M. C. and Meredith, W. J.: Dosage system for use in treatment of cancer of uterine cervix. Brit. J. Radiol. **11**:809 (Dec.) 1938.
13. Harris, W. and Silverstone, S. M.: Radiation therapy for cancer of cervix with an analysis of fundamental dosimetry. J. Mt. Sinai Hosp. **14**:369 (Sept.-Oct.) 1947.
14. Hunt, H.: Personal communication.
15. Pitts, H. C. and Waterman, G. G.: Treatment of cancer of cervix uteri at Rhode Island Hospital; report of 293 cases with 5 year follow-up. Surg., Gynec., and Obst. **64**:30 (Jan.) 1937.
16. Idem: Further report on radium treatment of carcinoma of cervix uteri; 135 additional cases with 5 year follow-up. Am. J. Roentgenol. **43**:567 (April) 1940.
17. Corscaden, J. A., Gusberg, S. B. and Donlan, C. P.: Precision dosage in interstitial irradiation of carcinoma of cervix uteri. Am. J. Roentgenol. **60**:522 (Oct.) 1948.
18. Merritt, E. A.: Roentgen therapy of carcinoma in buccal cavity and of cervix uteri. Am. J. Roentgenol. **42**:418 (Sept.) 1939.
19. Erskine, A. W.: Evolution of an improved transvaginal speculum. Radiology **43**:170 (Aug.) 1944.
20. Wasson, W. W. and Greening, R.: Further observation with intravaginal roentgen therapy of cancer of female pelvis. Radiology **49**:452 (Oct.) 1947.
21. Sante, L. R.: Pneumoperitoneum as an aid in pelvic irradiation for carcinoma of cervix. Am. J. Roentgenol. **46**:689 (Nov.) 1941.
22. Nolan, J. F. and Stanbro, W.: Dosage calculations for various plans of intravaginal x-ray therapy. Radiology **49**:462 (Oct.) 1947.
23. Meigs, J. V.: Wertheim operation for carcinoma of cervix. Am. J. Obst. and Gynec. **49**:542 (April) 1945.
24. Taussig, F. J.: Iliac lymphadenectomy for group II cancer of cervix. Am. J. Obst. and Gynec. **45**:733 (May-June) 1943.
25. Read, C. D.: Role of surgery in treatment of carcinoma of cervix. Am. J. Obst. and Gynec. **56**:1021 (Dec.) 1948.
26. Swanberg, H.: Summary of results in radiation treatment of uterine cervical cancer. Acta radiol. **28**:554, 1947.
27. Meredith, W. J.: Dosage distribution and dosage in carcinoma of uterine cervix. Radiology **54**:386 (March) 1950.
28. Arneson, A. N.: Radiation and surgical trends in treatment of cancer of cervix uteri. Am. J. Roentgenol. **59**:251 (Feb.) 1948.
29. Morton, D. G.: Pelvic lymphadenectomy in the treatment of cervical cancer. Am. J. Obst. and Gynec. **49**:19 (Jan.) 1945.