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## Prognosis of carcinoma of the uterine cervix prophylaxis, diagnosis, treatment

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THE PROGNOSIS OF CARCINOMA OF THE UTERINE CERVIX

PROPHYLAXIS, DIAGNOSIS, TREATMENT

Senior Thesis

1933

Angeline F. Simecek

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## THE PROGNOSIS OF CARCINOMA OF THE UTERINE CERVIX

Cancer of the uterine cervix kills 14,000 to 18,000 women in the United States every year (163). One woman out of every eight develops cancer, carcinoma of the uterus being the most frequent malignancy. Threefourths of all genital cancers are located on the uterine cervix. This malady represents about six percent of the average gynecological service.

These women are, for the most part, child bearing women or mothers who are rearing families and whose service is needed. There is absolutely no doubt that the woman who dies of carcinoma of the cervix has died, nine cases out of ten, because some obstetrician has failed to sew up a torn cervix or because some physician has failed to make an early diagnosis. A considerable proportion of the hopeless and far advanced cases are in these stages because of the ignorance and carelessness, not only of the patient but frequently of her medical advisors. It is a much greater crime that a woman lose her life with carcinoma of the cervix than a man lose his life with carcinoma of the lip. Lesions on the cervix can be plainly seen and felt in examination. The cancer can be diagnosed and treated, while it is yet early and curable. Proper diagnosis and treatment in the early stages will lead to cure while proper care after childbirth may prevent the disease.

There are certain factors in this disease that are not duly appreciated. It has a tangible etiology and a recognizable pre-cancerous stage, it is primarily accessible, it is to a considerable

extent preventable, and in its early stages, it is largely curable. The crux of the problem lies in prevention and early detection and both of these roads lead straight back to the medical profession; the achievement of both goals lies mainly in our hands. The chances of cure are directly proportional to the timeliness of the attack. The logical conclusion is that every cancer of the cervix passes through a period in its life history during which it is theoretically 100% curable. This is the rock on which the hope of controlling the disease is at the present time based. Ultimate success depends on the co-ordinated effort of every member of the medical profession who treats women at all.

It is difficult to realize how few incipient cancers of the cervix have until recently ever been detected and consciously treated. It is hoped that eventually the disease will be recognized early and this combined with our increasing knowledge of the behavior of cancer and our improved technique of treatment will increase our curability rate.

Sir Berkeley Moynibrans (135) says that by preaching the menace of cancer to the public we are not scaring the people to death, "we are literally frightening them into life".

To convince the profession and the public that even though cancer is apparently in the later stage of its development, if it is subjected to the proper treatment, its progress may often be stayed and the disease not infrequently cured; to make these facts so obvious that a general policy will be established to treat systematically every case of cancer, in whatever stage of advance, not only because of the immediate or remote possibility of a cure, but because palliative measures would bring great en-

couragement and relief of distressing symptoms; to establish a consciousness in the minds of all that cancer is curable, fear will be displaced by a spirit of hopefulness and every victim of cancer or suspected cancer will present herself for early diagnosis and treatment. (124)

The gynecologist should facilitate his instruction in diagnosis to the general practitioner, who may be taught to recognize a pathological cervix or if he cannot do so, that immediate consultation should be had. Delay for the purpose of observation is an error where carcinoma must be ruled out or in. If the beginning stage of cancer of the cervix were not devoid of symptoms, then the outlook for better end results of treatment would be encouraging.

The specialist sees relatively few early cases; the family physician many. Therefore, the prevention of cancer of the cervix as far as it may be possible by curing the precancerous condition is distinctly the duty and great opportunity for service of the family physician. The slogan for all lesions of the uterus should be "Early diagnosis, thorough investigation, immediate treatment". (118)

## INCIDENCE

Cancer is often called a disease of the menopause. Fifty percent of the cases appear at the ages of thirty-five to fifty, or on an average age of forty-three years. Thirty percent of the cases appear after fifty, with a few after sixty. The remaining twenty percent occur in women before thirty-five years of age, rarely under twenty-five. Bonner (17) reports a case in a thirteen year old patient; Glockner (171) in a patient, age seven; Gaughoffner, in age eight; Morse and McDonald in age ten and Scheffey in a twenty-two month old child (171). Hirst (93) states that malignant growths in very young are not so excessively rare and mentions a case of cervical carcinoma in a two and a half year old child.

In the Bucharest clinic (8) during the past ten years, the age incidence of the portio carcinoma has fallen appreciably, a fact which is attributed to publicity campaigns, resulting in patients coming earlier for examinations. Out of eighty-two cases seen between 1920 and 1930, fifty-five occurred in patients under forty years of age. The records also show that the age incidence of cancer development is lower in nulliparous women and those with few children than in those with more children but the number of cases seen is too small to allow of the conclusion that pregnancy protects against cancer.

It is probable that the greatest age incidence of thirty-five to fifty indicates that it is during that period that those irritative factors which gradually stimulate cancer growth are most likely to reach their culmination. In the vicious circle of nerve imbalance, the endocrine glands, the serum salts and the



psyche, constituting a systemic chronic irritation, is an influence in the systemic predisposition predisposing to cancer. The harmful influence of our modern civilization must be held to be perhaps one of the factors which are responsible for the prevalence of vago-tonia among civilized persons and which induce thereby the prevalence of endocrine and electrolyte imbalance. The universality of the observation of seemingly rising cancer incidence all over the globe would appear to directly postulate a predisposing factor of such general character as civilization. It would appear, then that the more marked potassium-calcium imbalance found above forty-five years of age in about seventy-five percent of those examined and the accompanying endocrine anomalies, both probably due to vago-tonia, not unlikely disclose the true inwardness of age, predisposition to cancer (209).

#### Incidence Following Pregnancy

There is a definite relationship between child-bearing and carcinoma of the cervix. The anatomical and histological changes leading up to cancer of the cervix are evidently connected with trauma incident to giving birth to children.

Penris (154) states that one must conclude that the percentage of nulligravidae amongst the cancer patients is lower and the average number of pregnancies higher than amongst women not suffering from cancer of the uterus. The association of a high incidence of carcinoma of the cervix with a low incidence of sterility is rather to be regarded on the outcome of some common factor, unspecified, than as a support of the traumatic theory of cancer.

Peller, (151) on the other hand points out numerous statistical

fallacies in attempting to prove that pregnancy favors the progress of cancer. He feels that pregnancy has a protective influence which persists after termination of pregnancy and becomes cumulative with repeated pregnancies. After the forty-sixth year of life, the protective effect of previous pregnancies against cancer appears to be masked by other factors which are not further defined.

Parturition, however, with its resulting damage to the cervix is generally accepted to be an etiologic factor in carcinoma of the cervix. The incidence of obstetric lesions preceeding cervical cancers is variously estimated to be from ninety to ninety-eight percent. Seventy percent of the parous and twenty-five percent of the nulliparous women have pathological cervices. This increases in importance with the number of pregnancies and the incidence is said to be higher in the poorer classes (181).

Something happens in childbirth that leaves an insult to the cervix that continues. The savage and Indian woman had no carcinoma of the cervix, states Dr. Quigley. There is some reason why a woman gets a tear in childbirth. Childbirth is a normal, physiological thing and should not bring any pathology or a pathological result. There must be something over looked in present day delivery which, if remedied would lead to a more normal physiological parturition and prevent cervical lesions that become malignant.

Foulkord (131) states: "An amazing personal experience of the past ten years is that since I have made rectal examinations entirely, I have found very few lacerations."

Bland (14): "The former practice of routinely submitting all patients to unskilled vaginal examinations during labor, with the

irresistible tendency to dilate manually and slip the attenuated cervix over the presenting part and incidentally traumatize the structure thereby, was unquestionably responsible for much cervical damage with its train of immeasurable sequelae. It is not possible to tell how much this wholly unnatural practice has cost in morbidity both immediate and remote. With less injudicious vaginal manipulation, both manual and implemental, so poignantly expounded in the teachings of obstetrics today the incidence of cervical injury should materially be reduced. Prevention rests more with the obstetrician than the gynecologist."

McGlinn (132): "Since high forceps are practically never used and midforceps but rarely, and large doses of pituitrin have been entirely discarded it is amazing how infrequently we see a lacerated cervix."

Longaker (131): "Another more important point is that ample time is given so that the cervix is not only dilated but retracted and the head completely extruded into the vagina before interfering instrumentally."

Quigley (163): "The bodies of women, dying of carcinoma of the cervix might be piled up in an enormous monument to the carelessness of obstetricians."

The frequency of the disease in comparatively young nulliparae suggests the probability of an hereditary factor.

## Hereditv

In considering the essential cause of cancer as a perverted biologic process, the question of a specific heritability immediately asserts itself. In a gross study of cervical cancer that has not extended far enough to obliterate anatomic landmarks, one finds certain typical characteristics. In the parous, the cervix is usually lacerated, irregular and scarred; the cervical lips are hypertrophied and everted, the muco-cutaneous border is exposed to traumatic friction from the vaginal walls with the production of erosions and heaping up of granulation tissue. The parts are constantly and for long periods of time bathed in a discharge that is chemically changed and irritating as the result of stagnation and infection. In the atrophic and nulliparous type, imperfect drainage is often present in some part of the genital canal, exemplified by stenosis of the cervix from ulceration, scar tissue or atrophy or by voluminous folds of the vagina, or by a scarred unyielding perineum or by an obstructing, rigid hymen.

Why is it that many patients with lacerated and ulcerated cervixes never develop cancer? Why, on the other hand do a few develop it so soon after the primary injury and why do young nulliparae with little or no observable irritative changes occasionally develop and apparently spontaneous growth? It is difficult to answer these questions on any other ground than that of inherited susceptibility. Artificial cancer is more easily and quickly produced in animals with a known cancer inheritance than in non-cancerous.

Waealer, (202) However, believes that the heritable anlagen play a part which is certainly not unimportant while at the same time the share of this factor in the classical trinity of disease

producing influences is not paramount. "Both the arithemitical analysis and the critical discussion confirm the impression that any simple Mendelian interpretation of the phenomena is impracticable."

Mme N. Dobrovolskaia-Zavadkaia, (49) also believes that "the different histological types of tumours are probably dependent on different genes in germ plasm and most certainly all kinds of chronic irritation contribute to the development of cancer in predisposed organisms and determine its localization."

Hartman(78) states, "Clinical and experimetnal work would seem to show that heredity plays a considerable role and that the inherited factor is a predisposition."

MacFarlane (131) gives a family history for cancer in eighteen percent of the case reports.

Experimental work along this line has been done by Maude Slye. (72) (179). Starting seventeen years ago with a strain of mice susceptible to spontaneous cancer, Slye has inbred them selectively through many generations and she has shown that inheritance of cancer character follows Mendelian law as closely as does that of alinism and pigmentation. Her work and that of others seems to prove beyond doubt the existance of an inheritance factor in mouse cancer. If the laws of phylogeny be accepted, the conclusion can scarcely be avoided that a similar factor must exist in varying degree of intensity in the entire vertebrate family, including the human race.

The work of the Sprague Memorial Institute, where Slye's experiments have been carried on has enabled Will to lay down the following dicta:

1. Cancer in mice appears in most of the forms seen in man and in far greater variety than had previously been supposed.
2. The tendency to develop cancer or capacity to resist cancer is unquestionably influenced by heredity.
3. Not only the incidence of cancer is influenced by heredity but also its site and its character and behavior.
4. The resistance to cancer in Slye's mice behaves in breeding like a typical Mendelian Dominant characteristic. The susceptibility to cancer behaves as a Mendelian recessive.

It would seem then, that certain women have inherited such a susceptibility to the disease that a cancer is more or less inevitable somewhere, and especially in a locus like that of the cervix which is normally exposed to irritation. This would explain the occurrence of cervical cancer in young people and soon after a child bed injury and in nulliparous women with slight erosions or impairment of drainage. On the other hand severe lacerations of the cervix in a non-cancerous individual might never cause a cancer or at least not until after a prolonged period of irritation.

Heredity as an influence in the systemic predisposition to cancer and on the elimination of cancer from the human race by means of selective breeding is most important. A patient may be robust perhaps and apparently healthy and appearing neither subjectively nor objectively to be in need of medical care, yet a patient because presumably her capacity to react to injury with prompt healing is impaired--a predisposition to cancer.

### The Precancerous Cervix

The time to cure cancer with greatest certainty is before it starts. There is no one great initial cause of cervical cancer. As far as this carcinoma is concerned, Bailey (9) believes that the initial causal factor concerned in the production of the intermediate causal factor is bacterial and is moreover concerned to a large degree with well known septic organisms. Recurrent attacks of specific intensity from the epithelial standpoint involving epithelium during the danger period result in the production of cancer. The question of time at which this attack is made, therefore plays its part and this fact is undoubtedly instrumental in minimizing this catastrophe. Cervicitis, erosion of the cervix is definitely related to carcinoma of the cervix. This relationship is effected thru the agency of a factor common to both - an associated inflammatory exudate in contact with epithelium. This is the intermediate causal factor and is constant.

C. H. Mayo says: "The part played by chronic irritation in the development of cancer is positive and definite to a degree. The danger of cancer is increased by all irritation and traumatism which demands a continued cell repair and it is in proportion to that demand." The beginning of carcinoma occurs in the region of the external os.

Virchow (72) first promulgated the hypothesis that cancer is the result of chronic irritation. Billroth announced that without chronic irritation, cancer does not exist. That traumatism and irritation may be factors in the etiology of carcinoma has long been a matter of observation. The irritation theory was held for many years as a hypothesis but was not confirmed by experimental proof until the second decade of this century. The pioneer work in this

field is credited to Fibiger who in 1914 produced cancer in the stomach of rats by feeding them with cockroaches, infected with round worms. Scientific research has led to warrant the conclusion that clinical and experimental evidence undisputably proves, that tissue cells, at least in certain individuals and localities can be excited to malignant growth by trauma or prolonged irritation of mechanical, bacterial and chemical influence. From a practical standpoint the known law of the causation of cancer, though it does not completely solve the problem, is of the greatest value to the clinician in this combat with the disease.

Chronic irritation may interfere with cell functions (149). Irritated tissues may lose all of their function except the more fundamental power of growth and reproduction. A pathological cervix is usually a focus of infection and is the most frequent example of a precancerous lesion. The eradication of an existent infection is the sound basis of future health and happiness. (130) In China, Japan and the Hawaiian Islands, the amount and virulence of the carcinoma of the cervix are outstanding. Among the etiological factors the most important seems unquestionable to be poor care or lack of care at confinement and in the post natal period.

The parasitic origin of cancer dates from ancient times. The very word "cancer" denotes a crab. In more recent times, there is the admirable work of Gye, who believes that the stimulating virus of cancer is due to an invisible filtrable bacterium.

Saunders (169) has isolated a streptococcus from the diseased conditions of the stomach, colon, breast and cervix. This organism is closely related to and identical with the streptococcus lacticus of cow's milk. He has formulated a hypothesis that this organism



is concerned in the production of cancer arising on chronic inflammatory conditions at the above sites. He brings forward evidence in support of this hypothesis.

The prime factors that enter into a dangerous chronic irritation of the cervix are: 1. Eversion and erosion of the mucocutaneous border of the cervical lips. 2. A stagnant and infected leukorrhoeal discharge. 3. Malposition of the cervix that encourages abnormal friction and incomplete drainage of some part of the genital canal. Unskillful and ill-advised surgery of these parts is usually manifested by scarred and immobilized tissues, when they serve to exaggerate the natural dangers of the post-climacteric genital atrophy.

In a study of fifty cases of nulliparous women the records reveal in over thirty percent definite associated lesions of long-standing ulceration, of genital obstruction such as partial or complete atresias, of extreme atrophy and of fibroids, also early gonorrhoeal infection of the cervix or of vaginal erosions that result from a misplaced uterus (72).

Transition to Malignancy has been found in the following lesions in the John Sealy Hospital (31): 1. Laceration of the cervix with cervicitis, with or without erosion. 2. Lesions, known as eversion, erosion, ectropion or exposure of epithelium to abnormal environment. 3. Chronic Cervicitis. 4. Adenoma of the cervix. 5. Adenoma of the endometrium.

Acidity is one of the requisites to the development of the cell proliferation we call cancer. (163) The injury done to the cell is not sufficient to kill it but interferes with its ability to do useful work. The time element must elapse between the insult to the tissues and the fully developed cancer.

The chemical reaction of the vagina is acid and that of the uterus is alkaline. The uterus is also sterile. The mechanism by which cancer develops at the cervix is as follows; "The external os is torn, everting part of the cervical canal lined with gland cells which normally live in an alkaline, sterile medium. Exposed to the acid and infection of the vagina, these cells die and a chronic ulcer is started. Infection ascends into the uterine cavity and an acid, irritating discharge results which prevents healing. The irritation eventually leads to cell proliferation and cancer. The time period may be many years." (163)

Cancer may grow without mechanical irritation, without chemical irritation, without heat, cold or light irritation but no cancer ever grows without irritation produced by microorganisms. It is evident that cancer is not produced by any one germ but that any germ that may localize and colonize and maintain its existence in any part of the body may produce the necessary irritating toxins, and set in motion the chain of events that eventually become cancer.

Seemingly, then, there can be no cancer without a preceding precancerous state and no precancerous state, without previous injury to the tissue by a cancer inciting factor. Malignant tumours do not arise where the tissue is normal. Cancer never begins in a healthy spot. Gebele says: "First injury, next inflammation, and repair, thereupon cancer."

A precancerous state appears always to be interposed between the taking effect of the cancer exciting factor and the onset of the state of malignancy. During the precancerous state, the fate of the patient hangs in the balance. It is, therefore, of surpassing interest that the precancerous state appears perfectly amenable to

curative intervention. Of greater importance than to know how to treat an existing cancer would be the knowledge of how to prevent the development of a threatening cancer.

#### Cervical repair

In attempting to formulate an organized plan of prophylaxis the question arises whether preventive treatment of the cervix really prevents the disease or whether it is generally felt that it ought to do so. Graves found only nine cases out of 538 which developed carcinoma after cervical repair. In 4815 cervical repairs, only seven cases developed carcinoma (later report). In three cases, the pathologist had overlooked a carcinoma in the tissue removed by a trachelorrhaphy; or in 5000 cases of cervical repair only four developed cancer later. In two of these the disease was conceivably encouraged by an unskillful operation or at least might have been prevented by a skillful one. It cannot be claimed that these figures constitute a scientific proof of the prevention of cervical carcinoma by repair since it is impossible to gather a series of control cases for comparison. Nevertheless they are of value in supporting the belief generally held and now rationalized by science that timely reparative operations insure an effective, though not perfect prophylaxis against cancer. (72).

Failure to discover the three cases of existing cancer, made during routine examinations of tissues removed during cervical repair is another imperative warning to give accurate and timely attention to the injured cervix. Most careful and expert diagnosis of these tissues is essential.

In a report from The Free Hospital for women, (treated by Graves and Pemberton), Bartlett (10) finds 29.5% showed a previous supravaginal hysterectomy. Careful biopsy at that time might have

revealed the presence of the disease and led to earlier treatment of the carcinoma.

Routine microscopic examinations of curettings and trachelorrhaphy specimens found a detection of sixteen cases of early carcinoma.

Foulkrod (131) states: "As to repair during the childbearing period, I believe with many obstetricians that if we can cure the cervix by cauterization and leave the repair alone, we are saving women from caesarean section or a much more seriously lacerated cervix."

Longaker: (131) "It is the duty of the obstetrician not to discharge a woman until her cervix is free from erosion, healed, and the entire surface is covered with squamous epithelium to the external os."

McGlinn: (131) "I am firmly convinced that cauterization of the cervix or coning out of the cervix is far better than either repair or amputations of the cervix. I doubt very much if the routine repair of the cervix after labor is absolutely necessary. I make it a routine practice never to discharge a patient until the cervix is entirely healed."

Keller (110) : Prophylaxis includes treatment of every erosion either by the thermocautery or with silver nitrate or low amputation of the cervix in all cases in which the erosion does not heal."

Cooke (31): "Except perhaps in women under twenty five years of age, in erosion, ectropion and eversion, such lesions should be excised and examined histologically while adenomatous growths, bleeding erosions and ulcers should be removed radically as a prophylactic measure.

Rogge (167): found that in two cases in which he had excised

leukoplakias, he observed local recurrence within a few months. In cases treated by amputation of the cervix, no recurrence has so far been seen.

Spirito (186) admits that it is difficult to diagnose pre-cancerous lesions macro- or microscopically but advises portio-amputation in doubtful cases and states that he has never seen a case in which cervical carcinoma occurred after this simple operation had been done. He considers (187) that cauterization or operation (trachelorrhapy) to remove suspicious areas as being inadequate and urges the more radical measure of amputation of the cervix as being the best prophylactic measure.

Hinselmann (92) claims that plastic operations which do not remove the diseased tissue do not prevent the subsequent development of carcinoma of the cervix. In a large series of cases quoted, where amputation of the vaginal portion of the cervix or cauterization was carried out, no case of the development of cancer has been observed.

Bartlett and Smith (10) cauterized 1,700 cervixes from 1914 to 1929 and there was no cancer development. Deep radial cauterization with actual cautery is practiced and is considered a fairly sure prophylaxis against malignancy.

Schmitz (174) : "Radical treatment of chronic cervicitis constitutes the best weapon against cancer. Statistics prove the superiority of amputation and cauterization over trachelorrhapy in the prevention of cancer. The latter reshapes the cervix but does not remove all abnormal cell changes which are located in the transition zone between the cervical canal mucous membrane and the vaginal mucosa.

The colposcope has been found helpful in guiding the treatment

of erosions. (166) The cautery treatment, which at present may be called paramount is handled most successfully under colposcope control, it is stated. Not only is this true as to the extent of the erosion which is to undergo treatment but especially in the early detection of areas in which repetition of the treatment is needed.

Quigley (162) stresses amputation of the cervix. "It has usually passed the point where aseptic repair may be done. It is too deeply diseased for satisfactory healing to take place." He advises radium plus amputation, radium to kill out microorganisms which have extended the infection deeply into the structures of the uterus and as a method of precaution as we never know exactly when the lesion ceases to be ulcer and begins to be cancer.

Archibald Leitch (72) has made the important observation that cancer may appear at a considerable time after cessation of the irritant. Repair of cervical lesions in general is then to be advocated but their timely repair in particular. By timely repair is meant the proper treatment of the damaged cervix before it has had time to develop those changes the long-continued irritation may cause, from which may eventually produce a cancer. At just what interval after labor, routine repair of the cervix should be done is a matter for the individual choice of the obstetrician.

Treating of erosions or endocervicitis with palliative treatment as douches, tampons etc., is useless or little short of criminal. (163) Local palliative measures never afford more than temporary relief and there is no justification for their use here. Nor is there any justification in waiting the development of a sufficiently characteristic appearance to justify the clinical

diagnosis of carcinoma. A woman is under the threat of cancer all the time she is carrying a torn cervix. Examinations by poorly trained medical men or by irregular practitioners, such as chiropractors and osteopaths, do no good and may give the patient a false sense of security. Quigley, further states that the cervix is best repaired at the time of confinement or soon because if infection of these structures has taken place and continued for a long period of time, it is never again possible to bring back an absolutely normal condition of affairs.

With regard to leukoplakias of the portio and vagina, Reyne-mann (81) remarked that it is not easy to assess the relationship of leukoplakias to carcinoma because it may require years of observation to trace the ultimate fate of a leukoplakia. There appears to be little doubt that carcinoma arises as frequently from leukoplakias in this region as from those in other organs, but it has not yet been ascertained how frequently and after what interval of time, it arises. In any case, a leukoplakia when found should be at once excised and examined histologically. If it does not show signs of malignancy the patient should be kept under observation.

As long as we do not know the actual causes of cancer, the knowledge of precanceroses gives us the only means of practicing effective prophylaxis of cancer. It is generally easier and more certain to cure a precancerous condition than an already developed carcinoma. There is no way of measuring the probability with which a certain leukoplakia is not itself a precancerous condition, or an erosion as such, but are the favorable terrain upon which actual precanceroses can develop in the form of circumscribed ulcerations and proliferations.

### Subtotal versus Total Hysterectomy

From the results of recent inquiries at various cancer centers in France and from a review of the French literature, Monod (136) concludes that the occurrence of carcinoma in the cervical stump after subtotal hysterectomy is much more frequent than has hitherto been supposed. The proportion of these cases to the total number of subtotal hysterectomies performed varies from 0.5% to 6.5%. The cervix left behind is more liable to become cancerous than that of the intact uterus because in the former case the cervix is cut off from its natural connection, is scarred, and is often in a condition of adenomatous endometritis. Apart from the obvious remedy ("Totaliser la subtotale") the next best thing is to leave the minimal amount of cervical tissue behind and to make a biopsy of this in order to make sure that it shows no precancerous or cancerous features.

Treston (195) reports a case occurring twenty years after subtotal hysterectomy for fibroids in a Hindu multiparous woman.

Zampa (215) argues that since the operative mortality of total hysterectomy varies considerably according to the operator, it is unreasonable to urge that this should invariably be performed. It should certainly be performed, however, when the operator's mortality figure for the total operation is below 2% and also when the cervix shows signs of suspicious changes.

Out of 1804 cases of cervical cancer, Branscomb (21) reports 46 cases occurring on the stump left after supravaginal hysterectomy. Of these cases, 16 occurred within a year after the operation and thirty at a longer interval. These results show the frequency of such cases corresponds very closely with the increased risk of total



as compared with subtotal hysterectomy.

Cohen and Delporte (43) believe that this occurrence is not infrequent.

Pisan (159) says the risk of subsequent occurrence of cancer does not contraindicate the subtotal operations.

C.H. Mayo and C. Mayo Jr. (129) recommend a total hysterectomy or subtotal hysterectomy and then days later removal of the cervix, enucleation of the canal and destruction of the cervical canal by cautery. This does not increase the mortality and accomplishes all that is desired. Subtotal hysterectomies should be watched. This is, no doubt, the wisest suggestion and plan.

#### Periodic Examinations

How may one find the symptomless clearly localized and nodular stage of carcinoma of the cervix? The profession should educate women to report for periodic health surveys after each labor and abortion and yearly thereafter (174). If symptoms of leucorrhoea, menorrhagia or irregular bleeding should occur the patient should apply immediately for an examination.

Enfield (57) states that it seems a radical suggestion and no doubt, for the population at large an impractical one, but the women whose social and economic status renders at all possible, should receive the protection to be obtained from a routine examination at least every three months from the age of thirteen on, whether there are any abnormal manifestations of any kind. It should be stressed to the general practitioner that the disease in its early stage is practically symptomless, that it is not limited to nulliparae and that it occurs frequently in the early thirties in women who have never born children, that the death rate

of cancer of the cervix could be reduced by nine-tenths if all women over the age of thirty submitted themselves to a routine examination once every three months.

Von Franque (200): "All parous women over thirty-five should be annually examined."

Ries (166) says in order to lessen the deplorable carcinoma mortality, even vaginal hysterectomy on every woman of carcinoma age has been suggested. "It would be entirely rational to invite all women to regular colposcopic examinations. These are simple, painless and require little time. A colposcopic examination must come to be a part of every periodic health examination, of every examination for life insurance and should be as familiar and routine as an urinalysis or blood examination." The colposcope, however, has the disadvantage in that it is an expensive instrument.

At least, periodic examinations of the pelvis during and after the childbearing period should be encouraged every six months in suspicious cases and once a year in others.

#### Legal Control

Legal intervention has been suggested by European Writers. d'Aprile (5) found a percentage of sixty-five for inoperable cases. Of the ninety-eight patients, twenty-seven had consulted doctors (five had not been vaginally examined) and twenty others had gone for treatment to midwives and apothecaries, for periods varying from several months to over two years. The author urges that the treatment by persons not medically qualified should be made a penal offense.

Dietrich (48) doubts whether compulsory notification of cancer

would be desirable. He thinks, however, that a legal control of institutions undertaking the radiological treatment of malignant disease is desirable and that the use of this method by unqualified might be forbidden.

Stauder (189) is opposed to compulsory notification of cancer, mainly on the ground of professional secrecy but is in favor of optional notification of cases on approved cards. He is also in favor of a confidential detailed death certificate.

Teschendorf (195) produces an excellent scheme for the establishment of cancer centres, but concentrates on radiological methods to the practical exclusion of surgical diagnosis and treatment and of specialists in various departments. There is an obvious importance in team work.

Holfelder (97) does not, on the whole favor the extensive establishment of these hospitals because he fears that this would eventually result in material for the study of cancer and the means of combating it being withdrawn from surgeons and students working in general hospitals and this would make difficult the active co-operation of the medical fraternity as a whole in the campaign against cancer. He believes this would be most unfortunate even granting that the assignment of cancer patients to special hospitals might result in improved diagnosis and treatment by a team of resident and visiting specialists in various branches of surgery.

#### Miscellaneous Factors.

F.R. Smith (180) finds that the average time between marriage and the end of the first pregnancy was 2.4 years in the cancer group and 1.4 in the controls. He compared the histories of 226 women with uterine cancer and those of 202 healthy women of about the same average age. All had had two or more pregnancies.

MacFarlane (131) found that in 66.6% of the cancer cases, the first delivery was more than two years after marriage. In 13.3%, the first delivery was before two years of marriage.

Fitz-Patrick (135) propounds the theory that a woman who persists in marital relations which reflexly cause in the uterus the changes incident to pregnancy but who at the same time repeatedly avoids child-bearing is misusing her organs and is not functioning physiologically. The virgin, on the other hand, even though she does not bear children is not malfunctioning.

#### Lysol Douches:

MacFarlane (131) reports the history of lysol douches in 49.1% of their cancer patients and in 18% of the controls.

Smith (180) found the use of lysol douches in 49.9% of the cases. Lysol is a saponified product of coal tar, the irritating qualities as to cancer production has been shown experimentally.

#### Dry Labors and Instrumental Delivery:

Instrumental deliveries and dry labors involving lacerations were commoner in the cancer group, as reported by Smith. MacFarlane found 60.9% of dry labors in the cancer group and 20.3% in the control group.

#### Leucorrhoea:

Leucorrhoea was more often noted in the control group but had been left untreated much more often in the cancer group. (Smith)

Menstruation is not shown to be a factor in carcinoma of the cervix.

#### Abortions:

The incidence of induced abortions with special reference to instruments might be an etiological factor. Liepmann (114) suggests

that a very important may be played by abortion, natural or induced and also by various physical contraceptive devices, especially intrauterine pessaries.

Contraceptives:

The types and duration of use of contraceptives as to possible influence on the cervical carcinoma is another field for further investigation. Dyas (54) reports the case of use of a metal pessary for seven years, with development of carcinoma. This illustrates the danger of the rather prevalent practice of introducing these substances into the uterus as a means of contraception. They usually produce the desired result but the case is proof that the method is too dangerous to be continued.

F. Delvaux (76) pleads for a systematic investigation of this mysterious immunity of the cervix to carcinoma in the presence of proclivitas and believes strongly that as a result of such investigation there would be a great advance in the discovery of the etiology of cancer.

The above factors at least suggest fields for further investigation by their possible etiological significance.

## SYMPTOMS

Carcinoma of the cervix is a peculiarly treacherous disease in that it does not cause definite symptoms in the early stages and because the first symptoms when they do occur, are not apt to rouse the suspicions of the patient or of her physician. The three cardinal symptoms are leukorrhoea, bleeding and pain, occurring in the order named. (72)

The disease is at first a building up or a piling up of new cells. When the new cells become so bulky that they can no longer sustain themselves, the exposed surface most distant from normal blood supply sloughs off and an ulcer or open wound is formed. As the front of the advancing cancer works itself deeper into the normal tissues and structures ( and it marches ahead through every living structure, even bone) the back sloughs deeper and deeper. Quigley compares this to a live parasite burrowing its way deeper and deeper, living and propagating and extending at the advancing margin while dying and carrying the virulent poisons of the dying and dead flesh at the other end. The slough eventually opens blood vessels which increase in magnitude as the slough proceeds. The original discharge robs the blood of calcium and the later bleeding robs the patient of a portion of whole blood. The patient suffers from: 1. General poisoning from infection and the protein poison and decomposing and rotten cell masses, 2. Loss of blood calcium, 3. Loss of blood. (163)

## Discharge

The vaginal discharge is due at first to an increase in the normal secretion, resulting from hyperemia and also to a secretion from the newly developed cells. At first, therefore, the vaginal

discharge of carcinoma differs from the normal secretion only in quantity and not in quality. Gradually, however, when the tumor growth becomes more permeable, the secretion becomes mixed with blood plasma and hence assumes a much more watery character. The watery consistency of the vaginal discharge is quite characteristic of carcinoma of the cervix and is one of the clinical signs that should arouse suspicion and urge immediate examination of the patient. Later, when necrosis of the tumor mass takes place, with a destruction of the superficial cells and consequent infection by various organisms of decomposition, the discharge becomes exceedingly foul and of a characteristic nauseating odor. (72)

Lupton (121) states that any slight increase of vaginal discharges should make us suspicious of carcinoma of the cervix.

#### Bleeding

Bleeding is due partly to an erosion of the capillary blood vessels by the action of the tumor cells and partly to trauma, by which the delicate papillary outgrowths are broken off during movements of the body, cohabitation, or digital examination. Thus it will be seen that the cauliflower type of cancer growing from the vaginal portion of the cervix would bleed more readily than the infiltrating form developing from the endocervix in which trauma would play a less important part. The cauliflower type is less treacherous than the other as it gives earlier warning of its presence by bleeding. Bleeding from cancer of the cervix is nearly always venous. Fatal hemorrhages are, therefore, rare. (72)

The ready bleeding of cancer of the cervix from coitus or digital examination is a most important sign, and does not often exist to the same degree in any other condition. It is often a late

symptom. It may be that the cancer cells have passed beyond control by the time the bleeding stage has been reached but on the other hand, some cases remain local a long time so that some of the cases that bleed are not entirely hopeless.

#### Post Menopausal Bleeding

Telinde reports that in 179 cases of post menopausal bleeding seen at the John's Hopkins Hospital (194) from 1919 to 1929, sixty were due to malignant tumors of the uterus. A particularly pernicious belief widely held among women of all classes is that bleeding often marks the onset of the menopause; more often it is the signal of well established and ulcerating cancer. (Ewing)

Kanter and Klawaus (107) found 51 out of 98 cases of post-menopausal bleeding were due to carcinoma of the cervix of 68.4%.

There are four types of bleeding: 1. Bloody stained leucorrhoea; 2. Spotting; 3. Moderate in amount; 4. Profuse with sizable hemorrhage and passage of large clots. The last three are most characteristic of carcinoma. All cases of postmenopausal bleeding should be considered as malignancies until proved otherwise. Once the menopause has been definitely established (no menses for a period of six months to one year) all bleeding from the genitals should be considered abnormal. There is no apparent relationship between the type or amount of bleeding and the seriousness of the existing condition.

#### Pain

The third cardinal symptom, pain is one of little value in making an early diagnosis as it does not appear usually until the case has reached an advanced stage. This is due to the fact that the cervix is a peculiarly insensitive organ so that while the dis-



ease is confined to the cervix itself, the patient experiences no pain, whatever. When, however, the cancerous process has invaded the parametrium or has metastasized to the regional lymph glands, pain ensues, and as the disease advances it may become excruciating. Unilateral pain in the lower back near the ischiac region is quite characteristic. Although the presence of pain usually signifies an incurable case, there are exceptions to the rule. (72)

Cancers have no nerves. They grow around and enclose the nerves which are already present in the tissues that they invade but no new nerves are grown. The tumor cells do not irritate nerves in such a way as to produce pain until the cancer masses grow so large and get so deep that they make pressure on the rather large nerves or nerve trunks. (163)

#### Secondary Symptoms

To the characteristic primary symptoms should be added the secondary or accessory symptoms: 1. From invasion of adjacent organs; 2. From compression of neighboring structures; 3. From toxemia due to septicity of the cancer; 4. From the cachexia occurring in all chronic and wasting diseases. (173)

#### Bladder Symptoms:

A cancer situated on the anterior lip of the cervix tends to grow toward the vagina and to invade by extension the bladder wall, giving symptoms of cystitis. In many cases, this is a late symptom but the invasion may occur while the case is still operable. It is a serious complication, however, and in general makes the prognosis as to recurrence particularly bad. The symptoms include: dysuria, polyuria, hematuria or pyuria.

### Ureteral Symptoms:

Implication of the ureters by extension into the parametrium may cause symptoms of hydro-ureter and hydronephrosis, due to mechanical obstruction of the ureters, with deep constant unbearable pain in the side affected. Wertheim (72) has shown that the ureteral wall is peculiarly resistant to invasion of cancerous disease so that symptoms are due to external pressure from the surrounding new growth masses.

### Rectal Implication:

Implication of the rectum is comparatively rare and occurs only in the most advanced stages. Symptoms are tenesmus, discharge, bleeding and ribbon-like stools.

### Pelvic Inflammation:

It sometimes happens that infection from cancerous growth especially of the infiltrating endocervical type in the posterior lip extends to the parametrium and pelvic peritoneum. Such infection produces the symptoms characteristic of a pelvic inflammation.

### External Genitalia:

In very advanced stages, the external genitals may become greatly swollen on account of thrombosis of the pelvic veins.

### Metastases:

General metastases to distant parts of the body are surprisingly rare and do not often occur even in the last stages. The three groups of metastasis are : regional gland deposits, retrograde deposits in vagina and vulva, distant deposits carried by lymph and blood circulation. In patients treated by irradiation alone, there was a strikingly large number of blood borne metastasis, is stated by Jeanneney (103). The frequency of metastasis is variously

stated by different writers as from two to eight percent. It is not increased by radium treatment, at any rate when precautions are taken to avoid local trauma and the application of excessive amounts.

From a histological examination of the regional glands removed in twenty-one cases of radical hysterectomy for carcinoma, Leidenus (119) found that only in six cases was carcinomatous tissue present in the glands. The other glands contained inflammatory tissue. Bone metastasis is rare. Tibia is involved more frequently than any other bone. Ford (66) believes that distant metastasis occurs more frequently than is ordinarily assumed. He states that pulmonary metastasis is not accompanied by any distressing symptoms so that only by frequent roentgenographic examination is it detected in the early stage.

#### General Constitutional Symptoms:

The general constitutional symptoms of advanced carcinoma of the cervix are especially marked by continued fever and by extreme cachexia. High, continuous and remitting fever, characteristic of sepsis and pyemia is to be referred to the activity of the bacteria which infect the cancerous mass. Sapremic fever with a lower pulse rate than that of the septic type is due to the absorption of decomposing cancer tissue. Irregular elevations of temperature are caused by the destruction and absorption of protein materials in necrotic fibroids and disintegrating hemateoceleles (Koblanck 72). Patients with advanced cancer of the cervix show marked improvement after radiation, of palliative operations, after curetting and cauterizing the excrescent masses, the improvement being largely due to the diminution in the amount of toxic absorption. Temperature elevation does not ordinarily appear in the

primary stages, so that it is of no great value in the making of an early diagnosis.

The cachexia that results from carcinoma of the cervix is extreme, being rarely equalled in any other form of cancer in the body, and is a fit setting for this gruesome disease. It is accompanied with great emaciation but neither cachexia nor loss of weight is apparent during the early stages. The causes which contribute to this cachexia are lessened nutrition from loss of appetite and hemolytic changes in the blood, due to toxic products from bacterial processes ~~for~~ from protein destruction.

Accessory symptoms are always suggestive of an advanced state of cancer and signify an absolutely poor prognosis. It may be stated that hemorrhage is the most early and most alarming symptom of carcinoma; discharge the most repulsive and constant symptom; and pain the most unfavorable symptom.

Miller says: (135) "Women must be taught that a vaginal discharge is never physiologic; that irregularities of menstruation are not normal at any age; that bleeding is not a natural accompaniment of the menopause; that neither discharge nor bleeding ever occurs from a healthy uterus when once menstruation has ceased; that pain is not an early symptom and that the woman who deludes herself with the belief that she has no pain, she cannot have cancer is going later to pay the price of her false security."

## DIAGNOSIS

The life of a patient with carcinoma of the cervix depends upon early detection of the disease. Since the cancer is always accessible mistakes in diagnosis should not occur if proper measures are observed. The requisites for making a diagnosis are, familiarity with the early symptoms and pathology of the disease, some experience in making vaginal examinations and a quick resort to biopsy if there is the faintest doubt. (72)

Early diagnosis has the obstacle in that it is so insidious and also in the widespread dread of operation. The full-blown carcinoma of the cervix is obvious. The fungating, easily bleeding, foul smelling mass of the everted type is simulated only by a necrotic pedunculated fibroid. Still more characteristic is the sloughing excavation of the ulcerated type with its hard, irregular edges and general infiltration and fixation of the surrounding tissue. In these advanced forms the pale watery discharge of pinkish or dirty hue, the unmistakable fetid odor, the anemic and wasted appearance of the genitals and the immediate profuse bleeding on touching the tumor are all signs each one of which is almost pathognomonic of the disease. But there are forms and stages of the disease which palpation and inspection cannot infallibly distinguish and the final diagnosis must be made with the microscope.

### Pelvic Examination

An early clinical diagnosis of cancer is largely a speculative matter, says Healy (82). The detection of early cancer is not a one-man job. It may require the cooperation of the patient, the family doctor, the specialist and the pathologist. It may, in some

cases be impossible even then.

Schiller found in serial microscopic examination of the cervixes of 135 uteri removed for various pathology but not cancer, four beginning carcinoma. One may conjecture therefore that 2.96% of carcinoma can probably not be diagnosed clinically by inspection. (174)

However, in the vast majority of cases, many cases of cervical carcinoma may be diagnosed from study made on a suspicious looking cervix, as detected by a pelvic examination. The equipment for a pelvic examination is simple. The diagnosis is often not made by many practitioners because they allow themselves to become too busy in their general practice to make a careful pelvic examination of every woman who consults them. Newell (147) stresses the importance of being "cancer minded."

In the early inverting form the cervical lip is hard, nodular, and irregular and usually bleeding a little on examination. The portio may be entirely intact and on inspection excite little or no suspicion. In elderly women, the atrophied cervix may have disappeared and in its place can be felt a stiff, nodular, puckering of the upper vault of the vagina. For the diagnosis of inverting carcinoma, the sense of touch is much more accurate than inspection. In most cases, a curet passed through the external os will bring forth a small crumbling bit of tissue with profuse, characteristic bleeding. If the curet fails to find friable tissue and the bleeding is slight, the case is probably one of atrophy or chronic cervicitis. The patient should then be examined under an anesthetic, the cervical canal should be dilated and specimens removed from the endometrium and cervix for biopsy. Such an examination is imperative not only for diagnosis but also to create

proper genital drainage if carcinoma is absent. (72)

Chronic cervicitis when the cervix is studded with deep lying Nabothian cysts often presents to the examining finger a suspicious, hard, nodular feel that suggests the inverting cancer. Lack of bleeding on touch, the absence of friable tissue, and the appearance of mucous on puncture of the cysts usually settles the diagnosis. If erosion and bleeding are present, no matter how slight, a biopsy should be made.

Early surface and everting carcinoma may have little or no induration but first attract attention by menorrhagia or metrorrhagia and by bleeding on coitus or digital examination.

On the other hand, non-malignant cervical erosions may bleed to the touch, cause metrorrhagia and simulate the appearance of an early surface cancer. Cases of this kind should always be subjected to biopsy for diagnosis. If cancer is not found the cervix should be regarded as in a clinically precancerous state and should be repaired by appropriate measures. The hypertrophied cervix should always be an object of suspicion. These cervixes may be filled with a cancerous growth which gives no sign due to a diminution in amount of toxic absorption. Temperature elevation does not ordinarily appear in the primary stages, so that it is of not great value in making an early diagnosis. (72)

Schroöder (178) found in 13% the epithelial proliferation characteristic of cancer of the cervix is localized in the form of exophytic, cauliflower-like carcinoma of the portio; in 43% as endophytic portio carcinoma which eats its way inward and has a tendency to break down superficially; in 9% as a deeply ingrowing cervical carcinoma; in 19% as cancer nodules situated

deep in the musculature of the cervical canal and in 16% as a greatly disintegrated crater following the breaking open of a cervical nodule.

#### Precancerous Symptoms

What should suggest the necessity of making a pelvic examination, other than the three cardinal symptoms, discharge, bleeding, pain? The precancerous condition may give symptoms for many years: Backache, headache, general muscle weakness and secondary anemia, symptoms due to absorption of micro-organisms and their toxins from the diseased uterus. Later, these symptoms become more pronounced and ulceration on the anterior or posterior lip takes place. (163).

#### Schiller's Iodine Test (74) (172)

Patients must be on the examining tables who without the impairment of health and often without symptoms harbor a disease which at the same time is invisible to the keenest eye and intangible to the most sensitive touch. The treatment of advanced carcinoma has actually reached an impasse. Surgery has attained its peak of usefulness. The limitations of radium are already in sight. There are then two primary needs for an early diagnosis of the clinically latent carcinoma. These are: Clearer knowledge of the histological appearance of an early carcinoma and some simple test by which the latent area may be accurately located for purpose of biopsy.

Schiller's conclusions are: 1. Carcinoma of the cervix starts in the squamous epithelium of the portio, near the os and at first spreads laterally, i. e. superficially. 2. It always starts in the unbroken epithelium and not in an ulceration. 3. Histologic-



ally, the chief determining points of 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.

But the histological revelation of the earliest appearances of cancer would be of little practical value without the ability to discover the location of a process not distinguishable by eye or touch. To meet this difficulty, Schiller has devised an ingenious test which bids fair to be of general clinical value.

The test is based on the discovery by Lahm that the upper layers of the normal epithelium of the portio and vagina contain rich masses of glycogen, which disappear when the epithelium becomes cornified or changed by cancer. In the normal living tissue, glycogen of the upper layer of cells is stained in a few seconds a deep mahogany brown by iodine in watery solution (Lugol's). A superficial area of early cancer being devoid of glycogen does not receive the stain and stands out startlingly white or pink against the deeply colored almost black background of normal tissue.

The test, simple as it seems, is not without its limitations. It appears to be completely reliable, when it is clinically negative, that is to say, when all the tissue takes the normal stain. The test is, therefore, specific for determining the absence of carcinoma of the portio and vagina.

But there are several conditions that obscure the test and with these the examiner should be thoroughly familiar:

1. The stain does not take on glandular epithelium like that of the endocervix. Hence an eversion would appear pink. The same is true of adenocarcinoma but fortunately this is rare.

2. Ulceration and erosions do not take the stain since they have no epithelial covering.
3. In areas of chronic cervicitis, the epithelium seems often to be deficient in glycogen, taking a very light brown, which with the surrounding deeply staining tissue, blends instead of being sharply defined from it as in cases of true carcinoma.
4. Normal stain is prevented or obscured by slight trauma such as that from tenacula or scrubbing with gauze.
5. The cervix and vagina of the hypoplastic and atrophic individual stains lighter than the normal. It is especially deep during pregnancy.
6. Pus stains black, since leukocytes are rich in glycogen. Necrotic tissue also stains black but clean, living granulations do not take the stain, a film of mucus prevents the stain. Blood and douche water obscure the reaction.
7. Hyperkeratosis prevents the stain as in leucoplakia, lues, and exposed areas in prolapse.
8. The test is limited in value in diagnosing advanced cancer, since the superficial assimilation stage is usually lost in the melleé of self-reproducing cells. Sometimes superficial areas detectable by the Lugol's test may be found beyond the border of the advanced cancer, especially in the fornices of the vagina and this may serve as a guide in determining the limits for a radical operation.
9. Schiller's test is specific for cervical cancer and is not adopted to other superficial cancers such as those of the vulva and skin in other parts of the body.

Application: A thick swab of absorbent cotton and gauze is prepared on the end of a stout wooden applicator. The swab is first

immersed in the Lugol's solution until a copious amount of it has been absorbed. With the upper vagina well exposed by speculum or retractors, the swab is then pressed firmly against the anterior lip of the cervix. The upper vagina is in this way flooded with the solution which instantly stains the normal tissues (excepting the mucous membrane of the endocervix) almost black. Any area of the portio, no matter how small that does not take the stain must be regarded with suspicion. The suspicious area is then curetted with a specially sharpened spoon curette. The strip of epidermis thus secured is placed immediately in hardening solution and sent to the laboratory for biopsy.

Schiller's test is an indispensable aid in the search for early curable cancer of the cervix. It is specific for the absence of cancer. Failure of the stain indicates certain other abnormal conditions, two of which, leukoplakia and intensive cervicitis are potential precursors of cancer and require treatment."

#### The Colposcope

The colposcope is the invention of Professor H. Hinselmann of Hamburg. It is constructed so as to give an enlarged stereoscopic picture. The instrument for use in offices affords enlargement up to tenfold. The colposcope has been improved and in its binocular form is made by the firm of Zeiss.

Since there is a group of surgeons who object to the exploratory excision as a possible cause of metastatic growth, the differentiation of benign erosion and carcinoma with the colposcope is most desirable. Leukoplakia is of sinister importance because of its connection with the growth of cancer. It cannot be diagnosed by palpation and is easily overlooked in ordinary specu-

alum examination. In fact, Hinselmann, (165) states that he had never seen a case himself before he used the colposcope, while in his report of June, 1929, he has accumulated 110 cases.

Pronai, Schauenstein, Kermauner, Schottlaender, Von Franque, Lahm and others have described a condition which they call "cancer surface coating" (Belag in German). It occurs in two forms, probably different stages of the same process. These surface coatings appear entirely different from the surrounding mucosa if observed with the colposcope (165).

Carcinomas have been described in early cases, the dimensions of which can be expressed in several centimeters, the smallest one known being 1 or .75. With a ten power enlargement, such as the colposcope affords, it is certain, that smaller carcinomas can be found. The principle advantage of the instrument is that changes in the surface are so minute that they cannot be felt and can easily be overlooked in the ordinary speculum examination but become plainly visible in the colposcope.

Lifvendahl (165) states that undoubtedly the instrument opens up a wide field for study in order to correlate what is seen through the instrument and what the pathologic findings are. It serves to concentrate our attention on the cervix in a more detailed and systematic fashion.

Hinselmann (174) records the following observations: 1. Normally the vaginal mucosa should end sharply and ringlike at the external os. Cancer is never seen in such cervixes. 2. An ectopic cylindrical cell mucosa does not predispose to cancer if the normal relations between vaginal and canal mucosa are maintained though they are misshaped. 3. If the cervical erosion becomes chronic and heals then a transition zone between the vaginal

and canal mucous membrane forms, in which nodules or erosions may be seen. He advises the colposcopic examination at three to four year intervals in all women older than thirty.

Saidl: " In the diagnosis of erosions the colposcope renders excellent service. It permits a differentiation between benign and malignant erosions. In malignant erosions, yellowish white areas, which are beginning necrosis, are seen on the surface. However histological examination is still essential for the diagnosis of malignancy as only future refinements of the method will permit an absolutely certain diagnosis to be made by means of the colposcope."

K. de Snoo (45), Schiller (172) and Martzloff (125) all emphasize the importance of the colposcope.

Graves (74) states that the invention of the colposcope by Hinselmann has been a laudable move in the right direction but that the instrument is expensive, requires expert manipulation and is not well adapted to the use of the general practitioner.

### Biopsy

Some writers emphatically state that the removal of cancerous tissue from a diseased cervix opens up avenues for extension and that this diagnostic measure should never be undertaken unless a freezing microtome is at hand and the patient is prepared for immediate operation. This fallacious and dangerous doctrine is losing its hold. Doubtful cases have been left to "see whether they develop cancer". The danger there is obvious. Dr. Greenough (72) writes, "I believe that biopsy is safer than delay." Drs. Leland, Regaud, share this view as opposed to Doederlein, Bowing, Oschner, and Lynch, who advise against any form of biopsy.

Tuberculosis, syphilis, diphtheritic patches, actinomycosis, condylomata accuminata, retained adherent placenta, endotheliomata, and sarcomata are all rare lesions that give symptoms and present appearances like those of cancer. Diagnosis is always made by the inevitable biopsy.

Novak (140) concludes that biopsy is not necessary if the cervix is of normal appearance; or if an area of erosion or eversion is pink, smooth, firm and non-vascular, without areas of either induration or friability. Biopsy is indicated if there is an indurated area on either cervical lip, especially if the overlying surface is granular, vegetative, or ulcerated, and very vascular. It is also indicated if, in an erosion or ectropion there is a hardened or raised area with vascularity, sponginess, or tendency to ulceration of the surface. The great majority of cervical lesions is obviously benign or obviously malignant, so that biopsy is necessary in less than 5 % of the cases. If the Pars vaginalis is normal in appearance, but the intracervical mucosa seems vascular or granular, the curette may reveal definite intracervical cancer, most often adenocarcinoma.

Novak advises that the tissue be excised from the most suspicious area, and the sections be cut in such a manner as to show the mucous surface. It is desirable to cut a number of sections at different levels in the block, he claims. The examination of the specimen should be made by a competent pathologist.

Von Franque (200): "The general practitioner should make a careful examination of every patient presenting symptoms even slightly suspicious of cancer and should then send the patient to a specialist rather than do a biopsy or curettage himself."

Epstein and Hedorejeff (58) : "The chief untoward results reported or feared in biopsy are infection, hemorrhage, and increased rate of tumor growth." They have reviewed the available literature and show that complications are the exception and not the rule. They consider biopsy is a safe and useful means of checking irradiation treatment.

Enfield (59): "The only method by which a case can be detected early enough is biopsy of small superficial erosions."

Quizza (37) agrees with most writers that removal of a good-sized wedge of tissue is necessary for biopsy.

Heidler (87) prefers a sharp curette for biopsy to the cutting out of a wedge because a large surface can be examined microscopically by curettage.

Schiller (172) prefers curettage with a sharp spoon to the excision of a block of tissue remarking that in cases of early carcinoma the superficial tissues show polymorphic and atypical cells.

Dyas (54): "The danger of biopsy, if any exists is far more than counterbalanced by the life-saving information it often yields.

It is permissible to conclude that in carcinoma of the cervix, a study of biopsy material will in about one third of the cases studied fail to indicate correctly the predominate variety of cancer cell in the parent tumor. Therefore any studies having biopsy material as their sole basis that attempt to offer a prognosis based on the predominant type of cancer cell face the problem of inaccuracy."

Graves (74): "The pathologist unfamiliar with the incipient cancer changes may miss the diagnosis or the operator may miss the cancer area entirely in removing tissue for biopsy."

Hellwig (88) says that under the best conditions an expert morbid histoglogist working in perfect cooperation with an intelligent clinician can provide definite information in 100% of the cases. "All dangers of biopsy can almost be certainly avoided if this procedure will be no more regarded as a minor operation?" The value of biopsy is only limited by the accessibility of the tissue and knowledge and experience of the pathologist. According to Bloodgood, the diagnosis of pathologic lesions through the microscope is largely a matter of memory and this requires special training and continuous operation.

Novak (141): "Certain benign lesions especially those of inflammatory character, not infrequently give rise to gross appearance which suggest malignancy so strongly that no clinician should be willing to assume the responsibility of making the decision without the aid of the microscope. The clinician aside from his general responsibility in the individual case must not only recognize when the help of the pathologist is needed but must collaborate with him by supplying tissue from which a diagnosis can really be made. In the overwhelming majority of cases, the diagnosis is reasonably plain from a clinical standpoint and in these the biopsy need not be done, or if it is resorted to, the evidence afforded by it will usually be only confirmatory. It need scarcely be said that the pathologist, no matter how expert he may be encounters his pitfalls, like his clinical co-worker. On suspicion, the biopsy should be repeated in two or three weeks unless treatment is imperative."

#### Sero-Diagnosis

Attempt has been made to identify specific changes in the blood serum of cancer patients with the object of finding a serodiagnostic



method for cancer. The work of the last ten years had proved cancer to be not a local disease but a general disease.

Treplin (35) believes that the following methods present a means of diagnosing cancer with certainty. He states that the diagnosis is quite certain when all three methods agree. 1. Extraction of fatty material from serum and obtaining a "cancer figure". It is stated that in all cases in which cancer was undoubtedly present the "cancer figure" exceeded 130. 2. Spectrometric examination. It is claimed that the serum of cancer patients gives a different curve from that of non-cancer patients. 3. Simple colloidal method for diagnosis.

Marzynskii (128) found that the serodiagnosis of malignant disease by a combination of Kahn's albumin A and Botelho's method gave true positives in 66% and true negatives in 80%. In the former series the presence of the malignant tumors had already been histologically proven by biopsy or operation.

Colorimetric serodiagnostic tests Revised by Savori (63) and modified later by him and Rebaudi gave favorable results with an enzyme reaction for the diagnosis of malignancy as reported by Figari. Both negative and contradictory findings with this test have been reported by Gerundo and others.

Witebsky (210): "While many of the diagnostic changes in the blood constituents found in various infective and metabolic diseases depend upon the presence of a specific antibody, no such antibody has yet been shown to occur in the blood of cancer patients." He believes that so far no specific serum test for cancer has been discovered. This is perhaps the consensus of opinion today.

Isaac (100) found that out of fifty cases of uterine carcinoma the normal sedimentation rates in 6 cases was present but

increased in 44 cases. He believes that there is almost invariably a direct relation between sedimentation rate and the stage of the disease, the rate being greater, the more extensive the destruction of tissue by the carcinoma and the metastatic invasion.

#### Urine Examination.

Hoffner and Buermann (96) state that they have applied to 624 samples of urine a test which promises to be of use in the diagnosis of malignant disease. It is based on the report of the occurrence of phymatorhysin and its prophase in the urine.

In the search for the early case it must first be recognized that the life history of a cervical cancer covers on an average from ten to twelve or more years. This includes a long, interval or irritative stage of chronic cervicitis, and a shorter though still protracted period of clinical latency during which the cancerous change though actually present does not attract the attention of the patient and her attendant. The careful clinician will be "cancer minded". He will make a careful pelvic examination and arrive at a diagnosis by the accepted methods of study: Schiller's iodine test, colposcope, or biopsy or a combination of these methods.

## TREATMENT

The keynote of all treatment of cervical cancer is an accurate determination of how far the disease has extended. When the growth is limited to the cervix the prognosis of an ultimate cure is excellent, but as soon as it has passed the boundaries of the cervix, no matter how slightly, the percentage of permanent cures begins to drop with great rapidity. Since from a practical standpoint the amount of extension of the disease outweighs all other considerations, the American College of Surgeons has adopted Greenburgh's classification in order to obtain a uniform standard of hospital statistics. This is as follows: (72)

Class A.: Disease limited to the cervix. At the Free Hospital for Women from 1875 to 1922, twelve percent of the cases were Class A cases. From 1922 to 1927, twenty percent belonged to this class. The five year cure was 52.7%.

Class B.: Disease has extended to the uterine body or to the vaginal wall. The importance of this tendency of cervical cancer to extend upward beyond the barrier of the internal os must be emphasized when radium treatment is used. In making a clinical classification of a given cancer, invasion of the vaginal wall is usually the determining factor for placing the growth in Class B. This may take place superficially from an everted cancer or may result from invasion of lymph spaces from an inverting growth.

Vaginal involvement occurs in nearly fifty percent of all cases; some authors make this figure considerably higher. Such an extension greatly reduces but does not exclude the possibility of cure. Up to 1922, Graves, reports that in 21.7% of the five year cures, rad-

ical surgery was done. Later statistics show that radium is more effective than the knife in Class B cases with vaginal involvement. A low invasion of the vagina precludes entirely the possibility of cure by surgery. It not infrequently happens in a case where both cervix and vagina are implicated in a cancerous growth that the point of origin cannot be determined. As cancer of the cervix is far more common than that of the vagina, the cervix, may in most cases be regarded as the starting point.

Involvement of the vagina sometimes takes place not by direct extension, but by implantation. This is uncommon as a recurrence after radium or operative treatment. Such metastases, though they appear to be implants, may nevertheless be the result of lymphatic transmission.

Class C: Disease has invaded the broad ligament, i. e., parametrial or paracervical tissue. The diagnosis of class C cases is made clinically by the ability to palpate indurated and fixed areas in the deep tissues surrounding the cervix. In well advanced cases, this method of diagnosis is fairly accurate especially if the digital examination be made per rectum. The possibility of such fixed indurations being due to an inflammatory parametritis is present but fortunately an error of this kind is not common because the simulating condition is relatively rare. The chief error occurs in classifying under A and B tumors that really belong under C. Sampson in 1904 showed that in many cases metastasis may lodge in the parametrial cellular tissue or glands which though demonstrable by the microscope cause no change in the tissues that can be detected by palpation. He also showed that parametrial involvement bears no definite relationship to the local size of the tumor. The figures of

those who have studied the parametrial extension by biopsy show a varying but always a large percentage of parametrial occurrence. Sampson found 46%; Wertheim 60%; Schottlander 75%; Martzloff 53% .

Parametrial invasion means low curability by operation. In Martzloff's series no patient with broad ligament involvement was cured by operation. Graves has a series of 2% of five year cures. Radium offers a better chance for patients in this class.

Class D: Disease has extended so as to produce wide fixation in the pelvis or has by direct extension of metastasis involved other organs, such as the bladder, rectum, regional lymph glands, and remote organs. Invasion of the various parametria surrounding the cervix may involve ureter, bladder, and rectum. The ureters lie in close proximity to the cervix so that direct extension readily compresses them, though it has little tendency to invade the ureteral walls themselves. Avoidance of injuring the ureters furnishes the chief difficulty in the radical operation for cervical carcinoma.

Rectovaginal and vesicovaginal fistulae or bladder and rectal involvement indicate an advanced stage of the local process. Fortunately this distressing phase of the disease is now for the most part avoided by the palliative use of radium.

The glands most often affected are the lower group--parametric, iliac, hypogastric, and sacral, especially those that are situated at the iliac bifurcation. More rarely the lumbar and even the inguinal groups may be the seat of metastasis. Often these glands show no external evidence that they are infected. On the other hand, large sinister-looking glands removed at operation often reveal no sign of carcinoma. Nor is the extent and size of the primary growth

a criterion for presence of gland involvement. A certain number of operable cases with gland metastasis are curable by operation.

Rarely tubes and ovaries are the seat of metastasis that reach them primarily through the lymphatics or possibly through the tube lumens. Distant metastasis through blood channels, as previously stated are rare and for the most part encountered in the late stages of the disease. The favorable locations for remote metastatic growths are the lungs, liver, kidneys, but they may appear in any other parts of the body, especially the brain.

Lynch (122) says, with evident rational, that the grouping of carcinoma cannot be standardized because so much depends upon the individuality of the surgeon. The cancer of a certain patient may appear to one well-trained surgeon as a definite example of one group, whereas another equally competent man may assign it to an entirely different classification. This is, no doubt true, but the classification of carcinoma of the cervix, has to some extent formed a basis for comparison of results, which would be a hopeless attempt were there not some foundation for the comparison.

Treatment of carcinoma of the cervix is at the present time entering upon a new and more hopeful phase. Much has been accomplished in the last thirty years in the combat against cervical cancer. It is treated by a number of methods that are chosen according to the extent of the disease, the available hospital equipment, and the individual skill of the surgeon.

#### Surgery

The radical operation, abdominal or vaginal dates from 1878. On account of its lower mortality, the vaginal route at first met with greater favor, especially among the surgeons of the continent.

Wertheim in the early years of the present century standardized the radical abdominal operation, greatly reducing the operative mortality and securing a percentage of permanent cures that had not before been attained. At the same time, Schauta was developing hysterectomy by the vaginal route and was able to show good results in a lowered mortality and improved percentages in five year cures. The vaginal operation was less available for advanced cases than the Wertheim method. The technique recommended by Wertheim was almost universally adopted by surgeons the world over, though with many individual modifications. Wertheim acquired great skill by operating on large numbers of patients and secured both a high rate of curability (42.7%) with a low mortality. Berkeley and Bonney, using a more extended operation than Wertheim were able to attain a high curability (52.7%) but with a greater mortality sacrifice. In the hands of Wertheim, Berkeley, and Bonney, and to these names must be added those of Bumm, Doederlein, Stoekel, Mayer, and Franz, the extended abdominal operation for carcinoma of the cervix may be said to have reached its peak of efficiency. Since the advent of radium, the formidable Wertheim operation has been losing ground.

The manner in which this has taken place is well illustrated in the Clinic of the Free Hospital for Women (72). Previous to 1921 cancer of the cervix was treated when possible by radical operation. At the time radium was used in Class A cases only when the general condition of the patient contraindicated surgery. At the present time, in Graves clinic radical operation is prescribed only in Class A cases and then only when the patient is thin and a good subject for surgery.

In many, probably in the majority of well-furnished clinics

the radical operation has been entirely abandoned partly as a result of the increasing effectiveness of radium and partly from the diminished surgical skill that lack of practice in this particular operation makes inevitable. (72)

Some of the men who have persisted to use surgery successfully are:

Auer (7) (1) : "Radical surgery proved superior to radium therapy in establishing a cure in patients in whom carcinoma was apparently confined to the cervix."

Deaver and Reimann: (42) give statistics to show that expectation of life is greater after operation than after radium or X-rays alone. From a pathologists point of view they conclude that the grading of tumors is misleading and unnecessary. They consider that extirpation as complete as possible should be aimed at, whether the disease is of low or high grade malignancy and whether it is more or less resistant to X-ray or radium therapy.

Adler (2): "Radical vaginal operation can be performed <sup>AND</sup> in a somewhat higher percent of the cases yields an incidence of absolute cure which is equal to that yielded by abdominal operation and has an operative mortality less than a third that of the abdominal operation."

The results of irradiation may perhaps approach those obtained by surgery but never surpass them. There is an advantage in post-operative irradiation! Adler introduces radium during the operation after closure of the peritoneum. This, he believes increases the percentage of cures.

Schroder: "It seems that the lower primary mortality of five to ten percent after Schauta's operation as compared with 19% after the abdominal operation is equalized by a higher incidence of recurrence following the former method."



Bartlett, G.V. Smith, and Philipp also report better results via surgery.

### Irradiation

This method of treatment of carcinoma of the cervix may include radium alone, Xray alone or radiation and Xray combined.

The first application of radium treatment of carcinoma of the cervix was made by Abbie of New York in 1905, but the credit of developing this form of therapy belongs chiefly to France. Dominic, Cheron and Rubens-Durrall gave the first report in 1913 and Friedrich and Kronig in 1914 and Kelly of United States in 1915. In United States, radium therapy has gained progress by work of Bailey, Kelly, Schmitz, Clark, Ward, Rauschoff, Healy and others.

Radiation as a means of combating cancer has made greater progress in the treatment of cancer of the cervix than in that of any other organ of the body. This success, as Regaud has pointed out, is due not to any specific radiosensibility on the part of the tissues involved but rather to certain favorable conditions of a local and anatomic nature. "It is because the vagina and above all the uterus, formed of fibrous and muscular tissues, thick, strong and radio-resistant, are able to support with impunity all kinds of treatment even when applied with bad technique. Moreover, the efficacy of radiation is principally due to the fact that the deep central situation of the diseased uterus is favorable for the employment of multiple cutaneous ports of entry and the convergence of the rays."

The radiologic treatment of carcinoma of the cervix is far from being standardized. Operators who possess only moderate amounts of the agent must adopt their treatment to their limited supply and

cannot conform to the standards of those more plentifully endowed. The technique of application of emanations differs from that of radium salts; the combined use of deep Xradiation, not available in many clinics, alters the methods of therapy. For these, and many other reasons, each clinic has its individual technique and ideas of dosage.

Methods of Treatment:

1. Intrauterine and vaginal Application is advocated by Regaud, and his associates, Proust and Denabids and Laborde. Five to ten milligrams of radium, screened with 0.8 mm of Platinum are inserted into the cervical canal. There are usually four tubes and are left for four to six days. The total average dose, then is 5,000 mg Hours. If the vaginal vault is involved in growth and the cauliflower mass present entirely hides the external os, or the cervix is represented by a deep crateriform ulcer, surface applications are employed.

The success of Curitherapy or Radium therapy for cervical carcinoma is due to anatomic relationship of the uterus and vagina, by which it is possible to apply radium in such a way as to exert a "crossfire" on the tumor mass. This is the very basis of all radiotherapy of deep cancer, direct fire being applicable only to superficial growths. The technique then is to distribute radium so that it will act (1), from the whole length of the uterine and cervical canal, (2) from the two lateral culdesacs of the vagina, (3) from the vagina. In this way the radiations are shot evenly through the cancer area, including the parametria with a maximum of "crossfire" effect. Much stress is laid by Regaud on application of the radium in the uterine canal.

2. Needling is a process whereby the cervix and lower segment

of the uterus are transfixed by needles containing two mg. and 1.3 mg. of radium, screened by 0.65 mm of platinum. Ten to fifteen needles are used, with a total of 35 mg. radium left in position for seven days. The average total dose is 6,000 mg. hours.

Interstitial radium therapy is employed commonly by those who have a limited supply of radium or for the reduction of large everting masses preliminary to a second deeper radium application. Regaud discourages the use of long needles placed into the parametria in conjunction with the utero-vaginal radium application.

3. The Intraabdominal application is supplementary to 1 and 2. There are numerous methods of applying radium to deep infiltrating cancer in the pelvis by approaching them surgically through the abdominal wall. Stanford describes the following method (29): A period of four to six weeks is allowed for cicatrization of the vaginal lesion. Laparotomy is performed in the Trendelenberg position. The lower half of the uterus is needled with six to eight needles of two mg. each, screened with 0.65 mm of platinum. The needles are placed anteriorly. The broad ligaments are incised, two or three tubes of five mg. each or one or two of ten mg. each screened with 1 mm of platinum, are placed on each side of the uterus in between the two layers of the broad ligaments. All needles and tubes have linen threads attached. These are enveloped in a sheet of thin rubber tissue. The abdomen is closed in the usual way. All threads and the end of the rubber tissue are brought out at the lower end of the wound. The radium is left in position six to seven days, and removed by traction on the threads, after removal of the rubber tissue. The average total dose is 5,500 mg. hours. In addition, Stanley Dodd and A. Goodman recommend the removal of

the iliac and obturator glands if removable and ligation of the internal iliac arteries.

4. The use of distant radiation with mass doses of radium requires a quantity of radium that but few clinics possess. The action is similar to that of the X-ray but whether or not it is superior in its effects has not yet been determined.

Dosage: Irradiation for short periods of time by large quantities of radium is gradually being superseded by prolonged irradiation with small quantities of radium. (29) The bomb method, in which five gr. of radium is applied daily for a short period may in the end prove the most valuable form of treatment.

Of the Coutard technique by radium application with small doses over a long period of time, Schroder (177) says: "The results so far are fairly good, fairly large recurrences have disappeared and in mass cases gross lesions have become smaller and more localized." He is of the opinion that this technique is a definite improvement and intends to continue using it.

Luppinger (120): "The Coutard technique although it has given successful results in the treatment of malignant tumors not amenable to other forms of radiation has not been generally adopted owing to the expense and time involved in its administration. The chances of cure depend on the presence or absence of metastasis and extent of growth. The general condition of the patient and the histologic structure of the growth are less important factors."

Results:

The immediate effects are: 1. Hemorrhage ceases, 2. Cauliflower growths disappear, 3. Ulceration heals, 4. General health of the patient improves.

End results: Heyman reports in 145 operable cases, a 46.2% cure.

### Histologic Types of Cells.

Carcinoma of the cervix exists in histologic types, which appear to possess varying degrees of malignancy. The adenocarcinoma is to be distinguished from the epithelioma or squamous cell variety. The epithelioma are divided into: 1. Spinous or typically epidermal type, 2. Irregular undifferentiated type, and 3. One that is intermediate (transitional). There is also the scirrhous form in which there is a predominance of connective tissue between cell nests.

It has been attempted to show that radium has a specific effect on these various types. Thus a cancer that yields readily to the influence of radium is said to be radiosensitive, whereas one that is less affected is called radioresistant. The establishment of a definite relationship between radiosensitivity and the histologic type of cancer would be of great practical importance both in the matter of prognosis and in the choice of certain lines of treatment. At this time, observers do not agree on the radiosensibility exhibited by the different cell types. Borst, Fischer, Mayer, conclude that the histologic picture is not a reliable basis for prognosis (72). Pemberton, and Smithwick in a review of radium cases, came to the same conclusion. Plaut goes still farther and even denies the existence of well defined groups according to the type of cancer cell (72).

It seems therefore, that with our present knowledge, the morphologic appearance of the cell has a limited practical value in prognosis in determining the particular modes of treatment. The most that can be said is that the malignant, very irregular, dedifferentiated cancers of the cervix probably are less favorable for radium than the more differentiated variety but this is due to the earlier

extension of the former to the parametria and lymph glands.

It is generally, though not universally, conceded that adenocarcinoma of the cervix offers a relatively bad prognosis for radium treatment, (Regaud, Adler, Proust, Lahm #2). Whether this is the result of a specific radioresistance or of its recognized malignancy and tendency to metastasize is not known. Regaud, here advises hysterectomy.

One of the first observations that every user of radium makes is that the everted (papillary vegetating cauliflower) growths are much more susceptible to radiation than the infiltrating variety. This difference is due not to an individual radiosensitivity but to the fact that the everted form is readily accessible, the inverting type having penetrated deeper into the tissues beyond a sure range of rays.

Another factor that seems to have some bearing on prognosis is the relative amount of connective tissue in the cancerous growth. The scirrhous variety is probably a less malignant type of carcinoma, the increase in connective tissue doubtless representing a form of self defense.

Comments on radium versus surgery are:

Swanberg: (195) "We believe that many operations called radical fall short of the best teaching regarding this operation and that relatively few surgeons are capable of performing a satisfactory Wertheim. The possibility of trauma, metastasis or implantation, growths must be borne in mind as well as the effects of prolonged anesthesia, loss of blood, hemorrhage, shock and other factors, contributing to a high operative mortality.

The general trend of the American surgeons is away from the

Wertheim type of operation. This is not based so much on its high mortality and morbidity as upon the study of end results, which show that when the disease has extended beyond the cervix and when metastasis has developed, the five year salvage is extremely small and does not overbalance the disadvantages of the radical procedure. On the other hand, if the cancer is confined to the cervix, the same proportion of cure can be secured by less hazardous procedure.

The radical abdominal operation has been thoroughly tried and at best the end results are far from satisfactory. From the anatomic standpoint, radical operation is hedged about with difficulties. The cervix is closely surrounded by vital structures, ureter, bladder, rectum, none of which can be sacrificed and injury to any of which is disastrous. The longer hospitalization and prolonged convalescence are also factors to be considered. Were it possible to show, however that the radical operation actually offered better results, this naturally should outweigh all other considerations.

It is among the Class A cases, that advocates of surgery still advise operation. The average operator, however cannot hope to secure the results of Von Franque (80% cures) and his results, even though in the earliest cases are probably no better, if as good as those secured by irradiation. A simple hysterectomy is of about as much value as no treatment at all (Wight). Weibel of Vienna who has perhaps had the most experience has a primary mortality of 13.8% and 40% cures."

Healy of the Memorial Hospital of New York says: "Hysterectomy is no longer justifiable as the treatment of carcinoma of the cervix, based on five year end results." (195)

Norris of the University of Pennsylvania: "A definite trend away from the more radical hysterectomy with its high operative

mortality and frequent postoperative complications can be observed in this country as well as abroad." (195)

Crossen of Washington University: "It is only occasionally that a case of carcinoma of the cervix is seen early enough to warrant operative removal, alone." He concludes that the important items in effective radium treatment are: 1. Careful study of special condition present in each case. 2. Maximum dose at first application. 3. Supplementary deep X-ray therapy. 4. Careful follow-up of cases and treatment of local spots and recurrences. (34).

Kelly of John's Hopkins: "On account of the numerous distressing recurrences even in this hopeful group (Class A) there is a growing inclination to decline operation in favor of radium. It brings promise of solace not only to the curable but to the incurable as well." (195)

C. S. Ward of Cornell University: "There is less primary mortality, less morbidity, less loss of time with radium than in the radical operation for carcinoma of the cervix. The palliative results in cases not permanently cured are an important advantage, not to be ignored. Large amounts of radium are not necessary to produce results. We believe that our results show that radium is preferable in all classes of cervical carcinoma." (195)

Ward and Farrar (206): "It must be borne in mind that if we give much larger doses of radium than are required to destroy the cancer cells, we shall also destroy the normal structures beyond repair and produce extensive necrosis with resulting septic absorption, hemorrhages and injury of adjacent viscera, with perhaps the formation of fistulas. The radiologist must work between the two extremes of radiosensitivity of cancer cells on the one hand and the normal tissues which are the seat of the disease on the other hand. If he oversteps



these bounds he produces either a so-called "primary acute radio-necrosis") or does not cure the condition, owing to a failure to destroy all the neoplastic tissue."

Regaud, Nogier, Delbert, Mocquot, Herrenschnidt and others have stated that if cancer cells are subject to insufficient radium to destroy them these tissues become radioresistant and this resistance increases with subsequent repeated and prolonged treatment until the tissues become sensitized. The so-called 'late reaction' of radium which is not manifest for six months to one year or more may follow.

"It is generally thought that the treatment should be completed in a relatively short time and should recurrence appear to regard radiotherapy as harmful and useless."

Schmitz of Loyola University: "If radiation therapy is employed on all cases, even in these of group one or Class A we will reduce the mortality and morbidity inherent in the surgical operation and definitely increase the number of five year good end results." (195)

Donaldson of St. Bartholomew's Hospital of London: "Carcinoma of the cervix is a comparatively radio-sensitive growth, and there are very few vital organs near which might be affected by wrong or at any rate inferior technique, so that good results have been obtained even by the most crude methods." (51) (195)

Findley of Omaha, Nebr.: "My own preference is for irradiation and irradiation only. There is: 1. Safety of irradiation, 2. Short period of hospitalization with little suffering, 3. Shortened convalescence, 4. Adaptability of irradiation to all groups of cancer. There is a tendency on the part of many medical men to regard radium as a drug with only one method of application. This is unfortunate for irradiation therapy but is doubly unfortunate for cancer cases." (64)

Wm Mayo of the Mayo Clinic: "Carcinoma of the cervix, even in the earliest stages is certainly as well treated by radium as by hysterectomy and in the advanced cases in which hysterectomy is not possible, radiotherapy will occasionally give splendid local results." (195)

James Masson of University of Minnesota: "Carcinoma of the Cervix always shows a high degree of malignancy and pathologically is very extensive so that most cases when they come for treatment are inoperable." (195)

Healy: "There are more specialists qualified to treat carcinoma of the cervix properly with radium and Xray than there are surgeons qualified to do a radical Wertheim hysterectomy. End results, on the favorable cases are, on the whole, somewhat better with radiation." (83)

The general opinion is that adenocarcinoma of the cervix is relatively insensible to irradiation but Le Maitre and Nuytten report a case treated by radium then deep Xray and no sign of recurrence eighteen months later. (114)

Lynch concludes that only the most radical of surgical methods together with radium compare favourably with radium alone as a means of treatment. (122)

Kaplan: "Experience has shown that the best results are obtained when radium is employed by one accustomed to this form of therapy and who has sufficient quantity of radium available. In the Bellevue Hospital, radium therapy has replaced operative procedures for carcinoma of the cervix and radium is also recommended as a prophylactic for precancerous conditions of the cervix. (108)

Shroeder concludes that the combination of the operation and irradiation has great advantages. (174)

Spinelli: "The best results from irradiation are obtained in large clinics where the treatment is given with good equipment and by experts." (185)

Stevens: "The foremost surgeons agree that carcinoma of the cervix is best treated by radiotherapeutic methods. Squamous cell carcinoma is ~~least~~ most resistant to irradiation and the most frequent in occurrence. Adenocarcinoma is the ~~most~~ least resistant to treatment and not so frequent in occurrence." (190)

Bowing and Ericke: report the rate of mortality in radium treatment as 1.06% among modified cases, 0.99% for inoperable and 0 for operable and borderline cases. (19)

Lupton recommends radium for borderline and advanced cases and states that there is a trend away from hysterectomy even in the early cases. He says that more and more radium is being used in the treatment of cancer of the cervix. (121)

Heyman: "Radiological treatment as practiced at the radium hemmet, in respect to absolute results in the treatment of cancer of the uterine cervix is superior to the operative treatment." (90) (89)

Mayo, Norris, Crossen, Kelly, Ward, Lynch (104) conclude in a report that cancer of the cervix in the earliest stages is certainly as treated by radium as by hysterectomy. "The opinions of these eminent men cannot be disregarded and it is reasonable to say that until some better treatment is discovered radium therapy is the best treatment for carcinoma of the cervix."

Jones: "Standardization of radium dosage for uterine cancer is impractical, dosage and technique must vary with character and location of the involvement." (104)

Zweifel: "The greatest advantage that irradiation possesses is that it is possible to cure a certain percentage of inoperable cases." (214)

Neill: "The value of radium treatment for carcinoma of the cervix is now well known and the results obtained in both early and advanced cases are superior to those of any other treatment."  
(144)

Quigley: "Most surgeons know that cancer cells will transplant and grow in any operative wound, yet very few guard against it. Most surgeons know that the lymph vessels in the cancer area carry cancer emboli, yet they fail to leave the wound open so that these cells can escape. The idea of surgery as the only remedy for all cases of cancer must be rejected as inadequate and often harmful.

Important factors in radium therapy are: 1. Safety in use, 2. Effect on Microorganisms, 3. Selective action of the radium rays.

Carcinoma is virtually liquid (a suspension of cancer cells in lymph around the margins of the growth) and this is transplanted and spread to great distance in the body by traumatism and manipulation.

Surgery is quite satisfactory in the cancer of the body of the uterus when the cancer is within the organ which can be removed or where the growth is within a capsule but not for the cervix.

The success of radium depends on: 1. The amount of radium used 2. Correct technique, 3. Kind of metal screen and thickness of screening, 4. Distance from lesion, 5. Time element, 6. Pathology of tissues being treated, 7. Anatomy and physiology of surrounding structures, 8. Accurate diagnosis.

We use no lead or other metallic screening to protect the upper part of the vaginal tract. For the purpose of keeping the tubes in place, we use only gauze packing. The reason for this, is that the

structures around the uterine cervix are traversed by a very rich lymph supply and it is necessary that all these structures come within range of the activity of our radium tubes. The use of lead may allow live cancer cells to hide behind the lead and so set the stage for recurrence. The material collecting in the bladder or rectum may push the wall of these structures a little nearer to the radium tubes and therefore no catheters are used." (163)

Contraindications for Radium: (195)

1. General emaciation and cachexia--treatment liable to result in rapid deterioration and early death. With a red blood cell count below 3,000,000 and a hemoglobin below forty percent, it is best not to use radium, which has a tendency to produce a greater degree of anemia, probably by a systemic action on the spleen and this in the presence of pre-existing severe anemia may be dangerous.
2. Pyonephrosis or hydronephrosis. The resulting increased fibrosis in the broad ligaments will add to the obstruction.
3. Rectovaginal or vesicovaginal fistulas. Here radium is apt to cause intense local irritation with sloughing.
4. If inflammatory pelvic lesion is present, radium will give massive necrosis with some toxemia and pelvic parametritis or peritonitis.
5. In massive extensive infiltration, radium may hasten rather than delay the end.
6. Impaired metabolism, especially a defective excretion of nitrogenous waste products.
7. Pregnancy (temporary), which should be overcome and then radium.

Preliminary Treatment: (195)

1. Examination and Classification.
2. X-ray therapy in more advanced cases.

3. Cervical Infection cleared--Copious, warm, mild, antiseptic vaginal douches several times each day.
4. Improve general condition.
5. Relieve Constipation.
6. Dilate cervix by graduated sounds and length of uterine canal verified.
7. Eliminate all forms of infection.
8. Radium Treatment: The patient is prepared as for a major gynecological operation with strict aseptic precautions, gentle manipulations, **A** general anesthetic is objectionable as it reduces the patient's resistance to cancer.

Post Radiation Treatment: (195)

The tubes are removed with the patient in Fowler's position. A hot sterile douche is used in a few hours. Boric acid douches are used daily for at least one month. The bowels are kept open and a good diet is important. The patient should report for an examination twice a month. Cervical stenosis with possible development of pyometria can be avoided by the passage of a uterine sound four to five weeks after treatment.

Reradiation:

Ward and Farrar (206) quote statistics which seem to justify repeated radiation. It is of definite value in local metastasis. An important point is frequent examination at regular intervals by the surgeon who originally applied the radium to ensure recognition of recurrences sufficiently early for successful re-radiation.

Auer (1) Believes that the repetition of irradiation is of considerable importance and should improve the survival rate.

Swanberg (195): "If the growth shows no response (rare cases)

further treatment is of no avail. If a large tumor mass has diminished at the end of two months but has not disappeared additional radium treatment will usually give good results. It is questionable however, if the typical complete treatment should be repeated."

Complications of Radium:

"It is necessary to have much experience to obtain from this method of treatment all the good that it may do without the evil that it may do." (Regaud 207). The safe employment of radium requires experienced piloting to avoid the damage that may be inflicted by over-radiation on the one hand and the failure to destroy the disease by insufficient radiation on the other.

The complications of radium are: 1. Hemorrhage--ulceration by radium, 2. Bladder and rectal symptoms may be early and late. It is reasonable to assume that if a sufficient dose of radium is given to cure carcinoma of the cervix it will also be sufficient to produce an erythema to the rectum and bladder. Very often this erythema is slight and passes unnoticed. It clears up in ten days to two weeks. 3. Late symptoms are difficult to differentiate from recurrences and this is very important. The symptoms are out of proportion to the findings. There is severe pain and tenesmus. The stool has blood and mucus. By digital examination, there is more pain than in a recurrence. There is no cachexia. By proctoscopic examination, there may be seen the scar or ulcer. This may take four to six months to clear up. 4. Fistula. (104)

Bowing and Ericke (19) state that treatment is halted at once at the onset of any of these accidents and is either abandoned or cautiously continued as the outcome warrants.

The gamma rays have a direct selective action on cancer cells. Lord Moynihan (207) has said: "The surgeon's knife in most highly

trained hands is an instrument of great delicacy, but it cannot always discriminate between healthy and diseased tissues, Radium is an instrument of far greater delicacy because its action is selective that is, to say, it acts differently upon the diseased and the healthy tissues, killing one and leaving the other." However, the safety of its use depends upon its proper employment. Treatment by a radiologist who has had a thorough gynecological training is the hope for optimum results.

#### Radium for Palliative Treatment:

Alvarez says: " The profession must be encouraged to take better care of the forgotten man, the patient with the inoperable carcinoma. Occasionally, to our astonishment, irradiation will even work a cure, when none was expected. " (124)

Donaldson: (51) "Many cases are so far advanced that they are incurable by any type of treatment yet devised but the palliation of such symptoms as pain, hemorrhage, odor, loss of weight and strength, fully warrant the radium treatment."

Schreiner and Kress (176) state that no other treatment could possibly have given the palliative results which are obtained in the incurable cases.

Let us say, then with Bloodgood(16): "My personal opinion is that the evidence favors radium treatment. Even when carcinoma of the cervix is discovered by biopsy only, radiations seems to offer just as much as surgery with less risk. The cure of carcinoma of the cervix depends upon the training of the surgeon and of the radiologist. It must be emphatically stated here that the danger of failing to cure a very early case of carcinoma of the cervix in the hands of an inexperienced and untrained radiologist is just as great, if not greater than the danger of post-operative death after Wertheim operation performed by an inexperienced surgeon."



## Xray

The explanation for the unsatisfactory results in treating even local and superficial cancer with Xray is that like heat or caustics the killing effect on the cancer cells is very nearly the same as the killing effect on normal tissues. Xray is of real value in connection with cancer as an adjunct or helper to other forms of treatment. Dependence should not be placed on Xray as a single remedy, says Quigley (163). It is excellent as a palliative for incurable carcinoma.

Stevens (190) reports a 32.4% cure with thorough irradiation of the pelvic contents with roentgen rays, followed by electrothermic coagulation of the malignancy and radium needles, with post-Xray again.

Pfleideier (156) also strongly recommends the pre operative irradiation or post-operative irradiation, with either radium or Xray. Preoperative irradiation transforms some inoperable cases into operable ones, sterilizes the growth, stops hemorrhage, improves the health and diminishes the operative risk. Postirradiation fibrosis is negligible if suitable dosage is given and if operation is not delayed more than one month after irradiation. Post-operative irradiation is a prophylactic measure to diminish the chances of recurrence.

Neill (144) however, believes that hysterectomy following radiation is not advisable and the use of Xrays to pelvis after local radium treatment does not appear to alter the prognosis. He believes that Xrays should be only used in the advanced cases as palliative.

### Miscellaneous Forms of Treatment.

The only forms of treatment that have stood the test of time are Surgery and irradiation, but numerous other methods have been tried:

#### Suprarenal Cortex Extract

The benefits of the use of the suprarenal cortex extract experienced by patients with malignant tumors, in relation to gain in weight, and relief from pain did not occur uniformly or in the majority of the patients observed. The extract administered to these patients had no selective influence on the growth, necrosis or sloughing of malignant tumors. Cure of malignant disease in patients with advanced cancer in view of the experience of the patients in these series cannot reasonably be expected to occur as the result of the use of suprarenal cortex extract. The benefits lie in improved appetite, improved muscle tone and bettered feeling of general well-being of patients who are ambulatory or who are not too far advanced toward a fatal termination of the disease. (80)

#### Cautery

Cautery has been used as a remedy in cancer because of its destructive action on living tissue; but in this destructive action, there is absolutely nothing selective. Healthy structures are destroyed equally with diseased structures.

#### Chemical Caustics

Chemical caustics have a destructive action and are favorite remedies among quacks. The action of these remedies on superficial malignant conditions is favorable only when the diseased condition is very thin and entirely on the surface. The worst phase of the paste cure treatment is the acceleration of the cancer growths. There is no field in medicine for treatment of malignant disease

by chemical caustics.

#### Extracts

In the treatment of cancer patients by cancer extracts given orally and applied locally, Curier and Carrere (29) do not give satisfactory information either clinically or histologically in support of even such slight success as they claim for this method of treatment. Nor is it apparent that their patients would not have fared better with surgical or radiation treatment or both.

#### Lead Treatment.

Lead, as well as strychnine (24) have been suggested as methods for cancer treatment. Maltina (123), Duhaill (52), Fitzwilliams, Crayer, Stone and others report on lead treatment but one is inclined to believe that the improvements are mere improvements in general well-being.

#### Acidification

Baumann and Bugnard (11 & 23) find blood changes in cancer patients, with a definite alteration in the hydrogen ion concentration towards the alkaline side. They suggest a trial of artificial acidification in conjunction with our present therapeutic measure as justifiable in inoperable carcinoma.

Perhaps one of the worst abuses of this intelligent age is the fact that so many of the patients with carcinoma resort to irregular practitioners who treat them with useless drugs, dieting, massage, heat in various forms, etc. None of the above named treatments have been established as recognized treatments.

Cordotomy for relief of intractable pain due to carcinoma of the pelvic organs has been done by Grant (71) and Resection of the

superior hypogastric plexus in case of uterine cancer by Percy (62) for the relief of pain. These are commendable suggestions, for it is a merciful act to rid these poor persons completely of pain, even though it subjects them to major surgery and a week of post-operative discomfort.

Hofbauer (94) maintains that irradiation of the pituitary gland, advocated by him has proved of great value as an adjunct to radium treatment of the uterine cancer.

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 that class. In cancer of the cervix, only the judgement and skill of the physician stand between the patient and certain death. Within a very limited time, the patient's survival is determined largely by the physician's judgement in the choice of remedy and his thoroughness in its application.

Moriarta (138) says that no one person is competent to carry on successfully and the only solution of the problem is by group study, and the ideal group should consist of a surgeon, a physician, a gynecologist, a pathologist and a radiologist.

## PREGNANCY AND CARCINOMA OF CERVIX

It is generally concluded that pregnancy stimulates the growth of an already present malignant growth. Morhardt (94) thinks that it is very significant that the cancer patient and the pregnant woman both have increased lactic acid in the blood and increased Prolan A in the urine and predicts that further study of these relationships will lead to valuable therapeutic and prophylactic discoveries.

Biro(13) found that in over 21,000 births during the last eleven years, only in eleven was pregnancy complicated by uterine carcinoma. All eleven cases were radically operated and seven showed three year cure.

In four cases, Adessi (1) performed hysterectomy or later when the foetus was viable this operation was preceded by caecarian section.

## CAUSES OF DEATH

Causes of death are found to be: (in order of frequency)

1. Cachexia, inanition, intoxication and sepsis.
2. Cancer itself.
3. Pneumonia and Pleurisy.
4. Urinary organs.
5. Carcinosis of pelvic organs.
6. Hemorrhage.
7. Cardiac disease, embolus of pulmonary artery, amyloidosis, purulent peritonitis.

# STATISTICS

## SURGERY vs RADIATION

	OPERATION	RAD.	OPER. + RAD	AV.
HEYMAN (90)	OPER. 18 - 20%	34.9%		
PHILIPP (157)	CASES 56.5%	27.6%		
LYNCH (122)	GROUP 1	100%	85%	LYNCH 19.3% CURE OF ALL CASES (148) NEWELL 22.4 (191) STEVENS 32. (72) GRAVES 19.3
	" 2	11%	53%	
	" 3	11%	33%	
	" 4+5	12%		
NEILL (144)	GROUP 1 11-18%	50%		
	" 2+4	16%		

## RADIATION

	SPIVELLI NAPLES	BEUTNER GENEVA	MUNICH	REGAUD PARIS	PEHAM VIENNA	PHILLIPS BERLIN	STOCKHOLM	BERNARD & BOWLING KRESS NY	FRICKE MAYO	HEYMAN RADIN MET	SCHMITZ HUEPER MERCY HOSP.	WARD WOMANS HOSP	PITTS WATERMAN RI. HOSP.	SCHERRY THYDUN JEFF MED COLLEGE
OPERABLE	58.1%	47.8	40.5%	42%	58.7%	50%	40.4%	62%	60.8%	40.4%	53.5%	57.1%	57.9%	100%
BORDERLINE	31.4	17.9	22.3	28	36.7	52	16	27						
INOPERABLE	2.5	15	16.7	10	9.9	16.6	20.6	13	ALL CASES 21.8	20.6	17.5	24.3	17.4	18.6
ADVANCED	2.8	2.7	1.2	0	1.8	16.6	20.6	1.1						

(185) ----- (170)

## 5 YR. CURES

AV. CURE - ALL CASES	20 - 25%
RADIUM - ALL CASES	33.4%
RADIUM - OP. CASES	54.9%
REST OF CASES	19.9%
SURGERY - OP. CASES	37.7%

Figures are very unreliable owing to personal factors--  
the skill of the operator, difference in pathological reports,  
methods of classification, but at least the radiological statistics are as reliable as surgery.

## CONCLUSION

A certain intelligent reformation of the habits of the human race must be accomplished before cancer prevention can show very tangible results. There is an immeasurable value in the co-ordinated effort among surgeons, pathologists, gynecologists, and obstetricians in the control of carcinoma of the cervix. A physician must also be taught that even when in a given case, the disease looks incurable there is always a gambler's chance that with the removal of the main growth health will return and the metastatic growths will be dormant for several years. A five year cure is wonderful but so also is a two or three year cure.

The cervix is the most neglected, most frequently infected and traumatized, most poorly treated and mistreated tissue in the female. "Every chronically infected cervix should be approached, then, not as a cervical catarrh, not as a hypertrophy, not as a laceration, but as the prologue of an epithelial drama whose curtain may be malignant death." Prevention, early diagnosis, immediate and proper treatment does much to cheat cancer of its potential victims.

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