THE RESULTS AND METHODS OF TREATMENT OF CANCER BY RADIATION

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(I) SURGERY AND CANCER.—That the most eminent surgeons of this country are interested in the hesitant beginnings of radiotherapy, and meet to discuss radiation in the treatment of cancer, is a manifestation the value of which is greatly appreciated by those who study this form of therapy. It is a great honor for the Fondation Curie and for its delegate to be invited to participate in these discussions.

It is at the same time an agreeable occasion for a radiotherapist to express his admiration for the progress accomplished in surgical technic and for the results of surgery in dealing with cancer. Also, I am pleased to recall here the names of certain American pioneers in this type of surgery, whose methods are now applied throughout the world. Among them are those of Halsted, the creator of the radical operation for cancer of the breast; the Mayos, who have transformed abdominal surgery; Cushing, who has created the surgery of the nervous system; Crile, who has perfected the technic of resection of cervical adenopathy; Graham, whose studies of operative technic for intrathoracic tumors give some hope in this domain; Bloodgood, whose works are appreciated not only by the surgeons, but by all cancerologists. Permit me to recall here a trait of Bloodgood's generous character. He was at one time skeptical of radiation. But when he began to realize the possibilities of radiotherapy in cancer, he was eager to manifest, in the presence of a large number of colleagues whom he had invited to his home, the new interest which radiotherapy henceforth held for him in the struggle against cancer. Several days after this memorable reunion, where he described his projects, death, which seems at times to wish to oppose human realizations, brusquely tore him from his work and from the affection of his family and friends.

(II) CANCER AND RADIATION.—Rich only in hope, possessing only incomplete information, incapable of offering precise technics, adapted to diverse types of cancer, radiotherapy has, however, obtained definite cures in cases incurable by surgery.

While surgery has applied its efforts with a certain regularity to all neoplastic localizations, radiation has, up to the present, been applied with success only to certain regions, in certain types of cancer, in spite of repeated attempts of treatment in all the histologic forms and in all localizations. Hence a primary classification of tumors in relation to the results of radiotherapy tends, little by little, to be established by regions, and according to a precise topography of the points of origin. Thus in the buccal cavity, the larynx and pharynx, there exist neoplasms of frequent curability, when

the origin is situated at a definite point. But when the point of origin is several millimeters distant, even though the histologic form is almost similar, failure is the rule. We shall later cite examples of this.

This empiric classification, when widely established, will give more living reality to histologic classifications, on which treatment by radiation was able, in the very beginning, to find a foothold, and will continue to strengthen. From the very beginning of radiotherapy, in the course of the year 1919 in particular, Regaud declared that radiation would be efficacious only in certain histologic forms. Without this scientific conception, without this foresight of facts, all progress would have been most difficult, and the discouragement in the presence of repeated failures in some histologic forms would have paralyzed for a long time the development of radiation.

(III) RESULTS OF RADIATION IN THE TREATMENT OF CANCER.—The patients who comprise the following statistics have been treated either by roentgenotherapy in our service, or in the ensemble of the different services of the Curie Institute, by association of radium and roentgen rays for the uterus and parametria, or by the association of radium and surgery for the tongue. Patients considered as cured have been followed for a minimum of five years. In fact, local recurrences have been exceptional after this period of control, but metastases by blood or lymphatic routes have not been rare after five years, when the neoplastic localizations were accompanied by adenopathy.

(a) *Lymphosarcoma of the Pharynx.*—We cite here statistics gathered by Doctor Jutras of Montreal, on the subject of patients treated, from 1923 to 1928, by roentgenotherapy in our service. Forty-six patients were irradiated; 16 have a minimum survival of five years, or 34 per cent.

(b) *Epitheliomata of the Palatotonsillar Region, Larynx and Pharynx.*—These statistics comprise the cases irradiated in our service, from 1920 to 1930, by roentgenotherapy. Sixty-six patients with epitheliomata of the palatotonsillar region were treated; 21 have a minimum survival of five years, or 32 per cent.

One hundred twenty-six patients with cancer of the larynx were treated; 31 have a minimum survival of five years, or 24 per cent.

Two hundred twenty-five patients with cancer of the pharynx were treated; 26 have a minimum survival of five years, or 11 per cent.

(c) *Epitheliomata of the Maxillary Sinus.*—At the Fondation Curie, the majority of epitheliomata of the maxillary sinus have been treated surgically, followed by application of tubes of radium in the cavity (method of Hautant-Monod). The results have been sufficiently satisfactory that the use of external radiation has in general been discontinued. However, when the extension of the lesions has rendered the cases totally inoperable, we have resorted to roentgenotherapy. The number of patients treated by roentgenotherapy is for this reason small. However, the results are favorable, and we have the impression that this type of cancer is among the most favorable from the point of view of roentgenotherapy.

From 1920 to 1932, eight patients with cancer of the maxillary sinus were treated by roentgenotherapy alone; four are still living, with a minimum survival of five years, or 50 per cent.

The first patient was treated in 1922, the second in 1930, the third in 1931, the fourth in May, 1932. Of these four cases, three had a total destruction of the floor of the orbit, and partial destruction of the malar bone; one of them had an extensive submaxillary adenopathy.

(d) *Epitheliomata of the Cervix Uteri.*—The statistics of cancer of the cervix are those of Lacassagne, which he has submitted to the League of Nations. They include all the cases of epithelioma of the cervix treated in the services of the Fondation Curie, by radiation, from 1919 to 1930.

Nine hundred eighty-four patients have been treated. Three hundred eleven have a minimum survival of five years, or 31 per cent. These cases are divided as follows:

Degree I, 97 patients treated; 59 having a survival of 5 years, 60%.
Degree II, 362 patients treated; 145 having a survival of 5 years, 50%.
Degree III, 411 patients treated; 101 having a survival of 5 years, 24%.
Degree IV, 112 patients treated; 6 having a survival of 5 years, 5%.

By years the extremes of results have been:

Degree I, in 1921, 14%; in 1929 and 1930, 72 and 75%.
Degree II, in 1919, 16%; in 1923 and 1930, 52 and 56%.
Degree III, up to 1921, 0%; in 1925, 1928 and 1930, 37%.

Up to 1921, cancers of the cervix were treated by radium alone, introduced into the uterine canal and vagina. In the course of 1922, the association of roentgenotherapy and radium began (the roentgen rays in general preceding the application of intracavitary radium), which has given, since 1925, 37 per cent five year survivals in Degree III.

In 1924, several patients with Degrees III and IV cancer were treated by roentgenotherapy alone, without intracavitary radium, as were those cases of postoperative recurrence. Sixty-three patients were thus treated by roentgenotherapy alone, nine have a survival of more than five years, or 14 per cent. Eleven were thus treated by Baclesse, in 1930; five are still living, or 45 per cent.

These results have been obtained with 200 kilovolts, while in general this voltage is too low to obtain cancericidal doses at a depth without provoking cutaneous injuries.

(e) *Epitheliomata of the Tongue.*—We give here the statistics of the Fondation Curie, comprising cancer of the tongue treated by association of radium puncture or intra-oral moulage for the primary lesion, with roentgenotherapy, radium or surgery for the adenopathy. These statistics are those of Roux-Berger, published in 1932, comprising the patients treated from 1919 to 1928. These epitheliomata are divided into three groups:

Epitheliomata of the dorsal anterior tongue.

Epitheliomata of the dorsal posterior tongue.

Epitheliomata of the infralingual aspect or floor of the mouth.

These patients are further divided into four degrees, according to the extension of the lesions:

Degree I, comprising lesions of 20 Mm. as a maximum.

Degree II, comprising lesions involving less than one-half the tongue.

Degree III, comprising lesions of more than one-half the tongue or floor of mouth.

Degree IV, comprising lesions involving the totality of the tongue or floor of the mouth.

Three hundred eighty-two patients have been treated; 71 have a survival of five years, or 18 per cent.

Among 198 patients with epithelioma of the dorsal anterior tongue, 45 have survived five years, or 22 per cent.

Among 91 patients with epithelioma of the dorsal posterior tongue, nine have survived five years, or 10 per cent.

Among 93 patients with epithelioma of the infralingual region, 17 have survived five years, or 18 per cent.

The dorsal anterior epitheliomata of the tongue have given 44 per cent survivals of five years for Degree I, 22 per cent for Degree II, and 10 per cent for Degree III.

The dorsal posterior epitheliomata of the tongue have given 25 per cent survivals of five years for Degrees I and II, and 14 per cent for Degree III.

Degree IV in these two localizations has given 2 per cent (1 in 60).

The proportion of deaths from adenopathy alone before five years, the primary lesion remaining healed, has been:

24 per cent for the dorsal anterior epitheliomata.
17 per cent for the dorsal posterior epitheliomata.
7 per cent for the infralingual epitheliomata.

The treatment of cancer of the tongue by roentgenotherapy alone has, up to the present, failed to give satisfactory results. It is, however, true that the patients treated were those having the whole of the tongue invaded, often with bilateral adenopathy, having Degree IV extent. Among 112 patients treated, only four have lived more than five years (3.5 per cent), and only nine have lived more than three years. In several cases in which marked improvement appeared to have been obtained, the patients have died of pyemia during the first year.

(IV) METHODS OF TREATMENT BY RADIATION.—(A) General Procedures of Irradiation: The exposé of the above results leads us to speak of the methods of treatment which were used. If one considers the situation of the source of energy, two general methods of irradiation exist:

The first is the method of irradiation by an internal source, the energy being introduced and maintained in a fixed position in the organism.

The second is the method of irradiation by an external source, the energy being outside the organism, the transfer of the energy being transcutaneous, through the tegument, which is the case when employing roentgenotherapy and telecurie therapy.

Each of these two methods naturally has its advantages, inconveniences and dangers, and each has an adaptation to particular localizations.

The first method permits the distribution of high doses of radiation in a short time, four to ten days, to the primary lesion itself, without too great damage to the general tissues, the volume of tissue irradiated always being small. Radium puncture in the treatment of cancer of the tongue or palate, intra-oral moulage in the treatment of cancers of the buccal surface, lips or floor of the mouth, and interstitial radium in the treatment of cancer of the breast are examples of this type of irradiation. Such is the treatment of cancer of the uterus by intracavitary radium utilizing very high doses. One can thus treat the primary lesion under ideal conditions provided the neoplastic mass is of limited extent, but one is obliged to utilize a second treatment, irradiation from an external source, or surgery, for the adenopathy.

The second method has the great advantage of making possible the treatment of extensive tumors, and in general the simultaneous treatment of the primary lesion and the adenopathy. It has the great inconvenience, in extensive or deep lesions, of necessitating fields of irradiation, or surfaces of entry of the rays, having a large area, and consequently irradiating a voluminous mass of tissue. In order to avoid general or local accidents, one is thus obliged to reduce the daily doses according to the area of the fields and the fragility of the organs traversed by the rays.

Meanwhile it is necessary to apply high cutaneous doses in order to attain a sufficient dose at a depth. The result is that the duration of treatment is always much longer with the method of external irradiation than with the treatment utilizing an internal source of energy. We have never obtained the cure of relatively superficial neoplasms, such as the larynx, in less than eight to ten days, and the skin modifications were always considerable when the duration of treatment was less than 20 days. When the neoplasms are more extensive and deeper, the treatment must extend over 30 to 35 days, and when it is a question of abdominal lesions (neoplasms of the cervix and parametria), the number of fields must be increased to six at a minimum, and the duration of treatment must extend to 50 or even 60 days.

(B) Generalities on the Biologic Effects.—The biologic effects are, on first appearance, the same after irradiation by external or internal sources. These are: (1) The destructive effects on the neoplastic cells, which one can observe conjointly with those produced on the normal epithelium of the mucosae. (2) The effects produced on the vasculo-connective tissue, or fibrosclerosing effects, which are at times followed by necrosis, early in the method of internal irradiation, and generally occurring much later in the method of external irradiation.

In reality the biologic effects differ widely in the time of their appearance. When one uses an internal source, with a high dose given in several days, the destruction of the neoplastic cells is most often accomplished *before* the appearance of the fibrosclerosing effects. Both effects are clearly ap-

preciable within the two weeks which follow the beginning of treatment. The early necrotic effect is generally of little importance. For example, in the intracavitary irradiation of the cervix, it is not exceptional to see a variable degree of necrosis of the submucosa or of the muscle itself, but considering the thickness of the cervix this necrosis is generally of little importance. Likewise, in the tongue and palate, the phenomena of sclerosis and necrosis, immediately succeeding the disappearance of the neoplasm, are of little importance. There persists only a more or less extensive shrinkage of the tissues.

When the irradiation utilizes an external source and must absolutely respect the tissues traversed, because of the extension of the neoplasm, the epitheliolytic effects are much later than in the preceding case. It often happens that the vasculo-connective fibrosclerosis *precedes* the cancericidal effects and thus suspends the neoplastic involution.

Suppose, for example, that we give the same irradiation by roentgenotherapy, with the same total dose, the same daily doses, repeated in a continuous manner each day for 35 to 40 days, to the buccal cavity of three different patients having an epithelioma of the palatotonsillar region. Supposing these three epitheliomata are of the same extent and aspect, but cover in one case the tonsil, in the next the pillars and the lower part of the palate, and in the third the base of tongue and the glossopharyngeal sulcus. The first two cases have a similar histologic form, cells having little differentiation; the third case is formed of more differentiated cells. The first case is accompanied by an extensive adenopathy, unilateral on the side of the lesion; the two other cases have no adenopathy. One might think that these three epitheliomata, quite close in structure, would react essentially in the same manner to radiation. In fact, when such lesions are of small volume and can consequently be treated by radium puncture, they are frequently curable; but the treatment by an internal source of energy brings to light no differences in their properties and their sensitivities to radiation. It is otherwise following treatment by roentgenotherapy. After 20 to 25 days of treatment by roentgenotherapy, there remains in the first case only a small, round neoplastic mass of one-half a centimeter in diameter, situated on the tonsil itself. It is the point of origin of the epithelioma. With the continuation of the irradiation up to about 40 days, the disappearance of this residuum is definite at about the thirtieth to thirty-fifth day, and the disappearance of the adenopathy will occur later, about the fiftieth day. In such a case a cure may be anticipated. We have patients of this nature in whom a cure has been maintained for more than five years, and there is no appreciable modification of the vasculo-connective tissue covering the tonsil.

In the second case, one likewise notes, toward the twenty-fifth day, that the tumor has almost disappeared, with the exception of small neoplastic nodules, nonconfluent, and only several millimeters in diameter. These nodules which, in general, correspond to the point of origin of the neoplasm and to the initial malignant cells, are *not* situated on the tonsil

as in the preceding case, but on the internal surface of the anterior pillar. Between the twenty-fifth and thirty-fifth days, one notes a transformation of the vasculo-connective tissue in the neighborhood of these small residual neoplastic nodules. The glossopalatine muscle loses its softness, becomes cicatricial, white, and deprived of vessels. This fibrosclerotic transformation is at times very marked *before* the disappearance of the neoplastic cells. One has the impression that a cure has been accomplished. But five to six months later, the pillar is covered with small multiple ulcerations, the recurrence is manifest, and rapidly assumes a necrotic character over a wide extent.

One is thus in the presence of two cancers of little histologic difference, as closely similar as to point of origin as it is possible to suppose, but different in the point of view of their manner of reaction to external radiation.

The third case differs further from the two preceding cases. Clinically the lesion extends more markedly into the glossomaxillary sulcus. However, as in the preceding cases, the greatest part of the neoplasm disappears after roentgenotherapy. There persists a tumoral residuum on the mucosa covering the internal surface of the angle of the inferior maxilla. At this point, where the vasculo-connective tissue more or less adheres to the periosteum, a cure has never been obtained.

In these three cases there is a slight difference in the histologic types, and a very great difference in the nature of the vasculo-connective tissue. When this tissue is loose, soft, elastic, as it is in the region of the tonsil or vallecula, the cure of epitheliomata arising in these regions is not difficult. But when the vasculo-connective tissue is dense, thick, matted, accompanied by muscular fibers, the tendency to fibrosclerosis is early and seems to *precede* the epitheliolytic effects. It thus seems that there exists an antagonism between "too early" fibrosclerosing effects and "too late" cancericidal effects. The more one tries to force the cancericidal effects by the augmentation of the daily doses, the more one intensifies the fibrosclerosing effects, thus reducing the nutrition and consequently the radiosensitivity of the neoplastic cells.

Thus the epitheliomata which have invaded compact bone, of which the periosteum is thick, serrated and dense, are among the most difficult to eliminate, and it is always at the site of bone involvement that recurrence occurs. Thus the epitheliomata of the inferior maxilla are in general more difficult to affect favorably than those of the superior maxilla.

The nature of the neoplastic cells and of the vasculo-connective tissue on which they develop are thus the two great factors determining success or failure in the course of irradiation by an external source of energy. It is in this manner that we are able to establish, little by little, according to the results obtained, an empiric classification of tumors according to their topographic and precise points of orgin. On the contrary, irradiation by an internal source of energy produces almost equivalent cellulicidal effects,

whatever the degree of differentiation of the neoplastic cells and whatever the nature of the vasculo-connective tissue.

One might thus be led to think that radiotherapy from an internal source could produce a cure in all forms of neoplasms of limited extent, and that radiotherapy from an external source could produce a cure in forms of greater extent and of slightly differentiated cells, developing in those regions having a loose vasculo-connective tissue. This is not entirely exact; radium puncture provokes quite frequently the appearance of adenopathy, and does so more frequently as the cells are less differentiated and hence have a greater tendency to local diffusion and dissemination by lymphatic routes. For example, the treatment of lymphosarcomata and undifferentiated epitheliomata by radium puncture has not in general given satisfactory results, except when preceded by external irradiation using large fields.

In résumé, irradiation by an internal source can be used particularly in the treatment of cancers of differentiated cells, of small volume, without adenopathy. Irradiation by an external source can be used in the treatment of extensive lesions accompanied by adenopathy, when the cells are undifferentiated or only slightly differentiated, and when the vasculo-connective tissue is soft, loose, elastic, nonfibrous, and not penetrated by muscular fibers.

These are the general rules based on the results obtained, when the method of external irradiation has been the most elementary, the least difficult—the method of continuous treatment. This is particularly simple when, for example, for a total cutaneous dose of 7,000 r/1,* the daily doses on the region of the neck are low (200 to 250 r/1), in order to avoid all excessive local and general reaction. But this method has never given us the cure of cancers of differentiated cells, developing on a dense fibro-connective tissue or having produced either muscular fixation, or adherence to bone or cartilage. In these cases the results are clearly improved when one strives to combat the early fibrosclerosing effects by the use of irradiation in periodic series, distributed at the moments of the maximum sensitivity of the neoplastic cells and not at those moments when the vasculo-connective tissue has a maximum tendency to sclerose.

The above exposé of the conditions of treatment and results concerns only the stratified epitheliomata, concerning which we have had a long experience. We shall now speak of the adenocarcinomata, which we know less well. It is more difficult to form an opinion on the effects of radiation in these tumors, because they have a different evolution than the stratified epitheliomata. The latter develop in essentially vital regions, such as the buccal cavity, larynx, pharynx and esophagus. They cause death in two or three years at a maximum, very rarely in more than three years, while the adenocarcinomata develop more often in less vital regions, and are in general less rapid in their evolution. Sometimes this evolution is very long, and one sees patients surviving after five years with neoplastic foci which have been temporarily arrested in their evolution by radiation. It seems

* r/1 (with backscatter).

that the effect of the fibrosclerosis which prevents the cure of stratified epidermoid epitheliomata, treated by external irradiation, produces in the adenocarcinomata quite different results. The cells of the epidermoid epitheliomata do not remain for long enclosed within this fibrous tissue; after several months they regain their development and a rapid recurrence is manifest. On the contrary, the cells of the adenocarcinomata are able to remain enclosed within this fibrosclerosed tissue for years, and it is only two, three or five years after the irradiation that the neoplastic cells of the adenocarcinomata appear to liberate themselves from this fibrous envelope. Ewing reports the case of a woman irradiated for a cancer of the breast and considered cured. She was killed in an automobile accident many years after her treatment. An autopsy was made of the previously treated breast, and groups of neoplastic cells, living enclosed within a fibrosclerotic capsule, were demonstrated.

In addition to these very slowly developing forms, one sees, but more rarely, adenocarcinomata of extremely rapid evolution, which cause death in less than one year, either by local recurrence after surgical intervention, or by the appearance of numerous metastases. These are generally very radiosensitive forms, reacting in a manner similar to the lymphosarcomata: it is among these forms only that we have obtained the definite disappearance of several apparently inoperable adenocarcinomata.

(V) Surgery and Radiation in Cancer.—(a) *Choice of Treatment.* According to the consensus of surgical opinion, all movable cancers, or all movable lymph nodes, are operable and must be removed surgically. One considers only the technical operability. But there exists another factor, which is the true or biologic operability, chosen or rejected according to the tendency to cellular dissemination and rapidity of cellular multiplication. The more embryonal a neoplastic cell, the more movable a cancer, the more the adenopathy is superficial and movable, that is to say, technically operable, as, for example, the lymphosarcomata or very undifferentiated epitheliomata, the less is the tumor biologically operable, because around these movable lesions, there are already isolated cells in the lymphatic chains. We could cite many observations in which a very movable tumor, having been operated upon, underwent a rapid cellular dissemination, followed in several months by an infiltrating and fixed tumor.

As far as radiation is concerned, the diagnosis of the degree of differentiation of the cancerous cells, and the knowledge of the degree of fibrosclerotic transformation of the vasculo-connective tissue, appear to be the basis of choice of the treatment applicable to a given cancer. When the cells are very slightly differentiated, when the cancer develops on a loose, nonfibrous tissue, when the cancer does not intimately adhere to the deeper planes, when it conserves a certain mobility, when it is not fixed to bone or cartilage, it reacts in general as a very radiosensitive tumor, that is to say, having a greater percentage of probability of being cured by radiation.

As we have explained above, due to the tendency of rapid cellular

multiplication and their immediate dissemination, this type of neoplasm is not generally favorable for surgery, even though it is technically operable. Moreover, such a tumor is generally rejected by the surgeons because it is most often accompanied by early adenopathy.

Cancers consisting of differentiated cells, developing on fibrosclerotic connective tissue, are the forms generally incurable or difficult to cure by radiation, because of their relative lack of radiosensitivity. When they are technically operable, they belong to the domain of surgery, because the cells multiply slowly, have only a slight tendency to dissemination, and develop an adenopathy only rarely or late. Such are the two extremes of cases.

(b) *Association of Surgery and Radiation.*—Between these two types of clearly defined cases, of which we have just spoken, there are an infinite number of intermediate cancers in which the diagnosis of differentiation and radiosensitivity is very difficult at present. In these intermediate cases, which are difficult to diagnose, the precise choice of treatment is less essential, and the association of surgery and radiation is often useful. This association will be necessary for a long time, because many cases will for long remain incurable by either surgery or radiation alone.

(1) *Preoperative Radiation.*—Radiation has for its principal effect the destruction of undifferentiated, young, neoplastic cells with a great tendency to reproduction; its effect is much less on the older and more differentiated cells, less able to reproduce. It thus easily destroys the cells most dangerous for the surgeon, leaving unmodified the cells of slower activity. When the surgeon is convinced of the necessity of operative intervention, and the tumor is not one justifying radiation, it would be rational to irradiate first, and operate later, because there is very frequently an association of young and adult cells. Each surgical procedure in cancer would benefit accordingly from preceding irradiation, sufficient to produce the destruction of all cells which are on the point of reproduction. This would give the surgeon added security in his operation. In such a case, it would be rational, in our opinion, to administer about one-half of the dose capable of arresting the neoplasm; for example, 3,000 to 4,000 r/1 on the skin, given slowly during ten to 12 days, with 300 to 400 r/1 per day, through two opposing fields. The surgical intervention could be accomplished before the possible appearance of new, young cells, that is to say, before the twentieth day, and in any case before the slight skin reaction of the twenty-fifth day.

If this treatment by radiation provokes a great reduction in the volume of the tumor, which is appreciable about the fifteenth day, one would thus have the proof that the cancer was very radiosensitive, very rich in young cells, and that surgery practiced at once might have been followed by recurrence at a distance, or by metastases. Thus preoperative irradiation in general assures more favorable conditions from the point of view of sur-

gery, and at times it is possible to identify a tumor which is biologically operable or inoperable.

In the case of a great and rapid reduction in the volume of the tumor, the treatment could be terminated either by surgery or by radiation, according to the speed of diminution of the neoplastic mass. On the other hand, if there is not a reduction in the tumor after two or three weeks, it is preferable to proceed with surgery.

If the tumor is originally inoperable, adherent, fixed to the deeper structures, and shows slight sensitivity to the rays, a partial treatment by radiation will, nevertheless, destroy a certain number of cells, liberate the neoplastic mass from its adherence for a limited time, and thus facilitate the surgical procedure from the point of view of technical operability, as well as from the point of view of the risk of dissemination.

(2) *Postoperative Irradiation.*—Postoperative irradiation may be either early or late. Early postoperative irradiation is preferably administered immediately after the healing of the tissues, about the twentieth day, while there still remains a slight degree of postoperative neoplastic activity, and while the cicatricial postoperative tissues have not as yet become sclerotic.

Irradiation is thus administered before the recurrence is apparent. But the recurrence is either certain, or only slightly probable. If the recurrence is certain, the surgical intervention being incomplete, the choice of the region to irradiate may be difficult if it concerns an extensive tumor having necessitated an extensive operative procedure, as, for example, an adenocarcinoma of the breast. It can happen that one may irradiate the region in which the recurrence will not take place. If the recurrence is only slightly probable, it seems preferable to us in this case also to wait, rather than to administer what is called prophylactic postoperative radiotherapy. A late postoperative irradiation, after the visible appearance or recurrence, seems to us preferable, as the radiotherapy is thus applied with precision over the zone where the cells are developing.

Insufficient, relatively slight radiotherapy has no other aim than to cause the disappearance of the most sensitive cells. It liberates for a time the neoplastic mass from the adherences which bind it, after which these may reappear and the tumor again become fixed and immobile.

If the radiotherapy has been complete, with a curative aim, and if it has not been followed by success, the infiltration of the tumor by the vasculoconnective tissue is much earlier, the neoplasm seeming to unite more intimately with the surrounding tissues. If it was mobile before treatment, it becomes fixed and infiltrating. This is one of the reasons why a second treatment by radiation has always been inefficacious, except occasionally when the tumor was very radiosensitive.

There is the same sequence after surgery, if the neoplastic extirpation has not been complete. The neoplasm becomes more infiltrating than before the intervention. The result is that, if one irradiates a recurrent cancer after surgical intervention, one rarely obtains the disappearance of the neo-

plasm, because the cells have a reduced sensitivity due to the cicatricial tissue and the increased infiltration.

Jolly, of the College of France, demonstrated 12 years ago, by a very simple experiment, the degree of reduction in radiosensitivity following the diminution of the nutrition and exchange. The thymus of the pigeon, lymphoid organ of very great radiosensitivity, is bilateral, and each lobe has its own vessels. If one ligates the vessels of one side only, and then irradiates simultaneously the two lobes, one notes the destruction of all the lymphoid cells of the lobe wherein the nutrition is normal, while the cells have been very little modified in the lobe in which the nutrition has been reduced by ligature of the vessels. These facts explain why, after surgery, as after radiation, cancers are less radiosensitive, since the section of the vessels and the fibrosclerosis diminishes the nutrition of the cells. Thus we have cures of recurrences after surgery only if the cells had originally a very great radiosensitivity, or if the treatment was practiced early after the intervention. But even though the radiotherapy has been early or late after the surgery, the disappearance of the neoplasm has at times been followed by quite extensive necrosis, which begins in the region of surgical section of the tissues, and appears one or two years later. Postoperative radiotherapy is thus in our opinion less efficacious than radiotherapy applied to nonoperated tissues; it is, moreover, somewhat dangerous for the general tissues, at least when it concerns stratified epidermoid epitheliomata.

Nevertheless, statistics published in various countries inform us that postoperative radiation has been practiced with a certain success in adenocarcinomata of the breast, even when preoperative radiation had already been administered. Preoperative radiation favors the production of fibrosclerosis, surgery accentuates it; hence these two transformations of the vasculoconnective tissue greatly reduce the radiosensitivity of the neoplastic cells. Moreover, the doses given in postoperative prophylactic treatments, or in late treatments, have in general been low, 500 to 1,000 r/1 to the region of the tumor. Even the cure of a cancer of the larynx or pharynx, or a cervical adenopathy, necessitates 4,000 to 5,000 r/1 directed over the neoplastic cells. One may thus be astonished that the cure of cancer of the breast and its adjacent adenopathy is obtained with doses of 500 r/1; moreover, these treatments have been able to be repeated with success, one or even two years later.

The ensemble of these facts is difficult to explain. Indeed, we have obtained the cure of postoperative recurrence of cancers of the breast only after doses of 4,000 to 5,000 r/1 on the neoplastic cells. In addition, during the course of numerous experiments, Regaud has shown that the disappearance of neoplastic cells of stratified epitheliomata, or of the normal epithelium of the testicle, have never been obtained by the use of repeated irradiation over one or several years. Moreover, he has shown that the parent cells of adenocarcinoma are in general less sensitive to radiation than the parent cells of stratified epidermoid epithelioma.

The opinion of Regaud, the case cited by Ewing, and several similar observations, in which the autopsies of patients treated by radiotherapy and apparently cured of adenocarcinomata have revealed neoplastic cells after five to ten years, leads one to think that the difference in sensitivity between the parent cells and the lineal cells is perhaps more marked in the adenocarcinomata than in the stratified epitheliomata. It would thus result that, in a certain number of cases, what had been considered as a cure would be only the destruction of the very fragile daughter cells; the parent cells, whose evolution is much slower, could remain enclosed within a fibrosclerotic connective tissue for a very long time. Whatever the reasons may be, it seems to us justifiable to draw the following conclusions.

CONCLUSIONS

A primary empiric classification of tumors as to their precise anatomic points of origin will constitute, for radiation therapy, a basis for prognosis and procedure, and will lend to histologic classifications greater utility in radiation therapy.

As far as radiation is concerned, the diagnosis of the degree of differentiation of the cancerous cells, and the knowledge of the degree of fibrosclerotic transformation of the vasculo-connective tissue, appear to be the basis of choice of treatment applicable to a given cancer.

In addition to the technical, or presumable, operability, there exists the true or biologic operability, which is one chosen or rejected according to the tendency to cellular dissemination and rapidity of cellular multiplication.

With the exception of very radiosensitive forms, relatively few in number, the cure of adenocarcinomata remains more difficult, and more rare, by radiation than the cure of stratified epidermoid epitheliomata.

Inasmuch as radiation has not as yet produced the cure of an appreciable number of inoperable adenocarcinomata over a period longer than five years, those which are technically and biologically operable should by preference be operated upon, as a rule, after a moderate external irradiation.

Cervical adenopathies in relation to highly differentiated epitheliomata of the mucosae benefit in general more from surgery than from radiation. On the contrary, adenopathies corresponding to neoplastic lesions formed of less differentiated cells belong to the domain of radiation.

In any combination of surgery and radiation therapy, it is, in our opinion, more efficacious to *precede* rather than *follow* surgery by radiation.

DISCUSSION.—DR. MAURICE LENZ (New York): It had been realized for a long time that large doses were essential for clinical arrest of cancer by roentgenotherapy. This could frequently not be carried out because of concomitant roentgen ray injury to adjacent normal tissues, especially in deeply situated and not markedly radiosensitive malignant tumors. Coutard reduced this handicap by applying to practice the principle of fractionating and protracting the total dosage over a longer period. This he did at the suggestion, and on the basis, of experimental work carried out on ram's testes by Regaud. In Coutard's method the entire amount of irradiation is given

over a period of several weeks, and the treatment is never repeated, thus taking advantage of the full resistance of the normal surrounding tissues and before retrogressive radiation changes have taken place in them. In cases of neoplasms of the upper respiratory and digestive tracts, this treatment produces such a severe reaction in the irradiated mucosa that it is temporarily denuded of its epithelium. The more important nourishing vascular and connective tissues, however, are conserved and the denuded area quickly epithelializes from the edges. Coutard has been able to arrest cancers which, up to his time, had been regarded as unsuitable for roentgenotherapy even by the most experienced radiologists. This he did by varying the daily and total dosage in accordance with careful daily clinical observation of the patient and prolonging the treatment over a period of several weeks.

Thus certain epitheliomata of the tonsil, pharynx and larynx have yielded a relatively high five year freedom from clinical evidence of cancer with his treatment, whereas this had occurred only exceptionally before his work became known. Successful application of his method has not been limited to himself, but has been repeated by all those who have followed his technic. For instance, there had not been a single instance of five year clinical freedom of cancer in those cases treated by roentgenotherapy at the Presbyterian Hospital of New York prior to 1931. Since we have applied the principles of his treatment, we have had a number of five year clinical arrests.

Roentgenotherapy as an addition to intra-uterine and intravaginal radium in cancer of the cervix, especially where the outer portions of the parametria are clinically involved, became important through his work and that of his associates, and was chiefly responsible for the remarkable increase in the number of five year clinical arrests in this group of cases at the Radium Institute in Paris. Roentgen ray injury to the intestines and bladder, which previously had frequently complicated the treatment in these cases, became rare.

In roentgenotherapy of cancer of the breast, which is still in its infancy, this treatment has already attained some importance as a preoperative measure, the operative removal being facilitated by shrinkage and increased mobility of the cancer. The two months' delay for preoperative roentgenotherapy certainly seems justified in cases with palpable axillary nodes, in view of the unsatisfactory, purely surgical five year statistics in this group of patients. The growth restraining effect of roentgenotherapy in inoperable cases is generally accepted. In postoperative roentgenotherapy the anatomicophysiologic conditions rarely permit the administration of sufficient roentgen ray dosage to allow hope of permanent arrest of all cancer cells; the aim of the treatment is not permanent arrest, but retardation of the growth.

Coutard has stressed the relation which exact anatomic location of the cancer has to its radiosensitivity and prefers to classify the radiocurability of his cases more in accordance with the point of origin of the cancer than purely on microscopic structure. The bearing which the condition of the vascular and connective tissue background has on radiocurability is illustrated by the three patients with squamous cell cancer arising respectively in the tonsil, the anterior pillar of the tonsil, and the mucosa covering the oral surface of the angle of the lower jaw. In the tonsil where the connective tissue is loose and elastic, the results are good. On the posterior or inner surface of the anterior pillar, the connective tissue is denser and the results are correspondingly poorer. On the inner surface of the angle of the jaw, the connective tissue is very dense, tendon-like, and arrest by roent-

genotherapy practically never occurs. Our own clinical experience bears out the correctness of these observations as far as the relationship between results of roentgenotherapy and apparent site of intra-oral origin is concerned. Coutard has emphasized the clinical significance of producing roentgen ray sclerosis in the connective tissue surrounding the cancer. If this change takes place before all cancer cells have been destroyed, further irradiation increases the sclerosis but does not destroy the cancer. This, for instance, is what happens in the epitheliomata located on the inner aspect of the angle of the jaw. It also happens when sublethal noncancer-killing doses are administered at long intervals over a year or two. On the other hand, in slowly growing adenocarcinomata of the breast, sclerosis of the connective tissue following roentgenotherapy may so encapsulate the cancer cells as to prevent their growth for long periods of time and thus help to lengthen the survival of the patient.

He has emphasized the need for close coöperation between surgeon and radiotherapist when decision is to be made whether a patient with a technically removable malignant tumor should be operated upon or in spite of technical operability would derive greater benefit from radiation or from a combination of both. Finally, he has again pointed out that roentgenotherapy of cancer is not a simple technical procedure which may be entrusted to the inexperienced hands of anyone possessing a roentgenotherapeutic machine. On the contrary, it is a difficult clinical treatment which is influenced by the anatomic extent and location of the cancer, by its microscopic structure and the radioresistance of the normal surrounding tissue, and presupposes not only adequate equipment and familiarity with roentgen ray physics, but, above all, clinical judgment based upon careful observation of the patient under treatment.

Professor Henri Coutard (Paris, France) closing: Roentgenotherapy of cancer of the breast is, and probably will remain, one of the most difficult radiation problems for a long time. Mitosis and cicatrization may take place concurrently in cancer of the breast, yet treatment should, logically, be carried out only when tissues are especially radiosensitive, *i.e.*, during the first of these processes. This is manifestly not practical since it is not known when these changes take place. Postradiation reaction of connective tissue to similar dosage varies considerably, as shown by studies of mastectomy specimens removed five, 20 and 30 days after radiation. Roentgenotherapy has usually been unsuccessful where the connective tissue has shown sclerosis prior to irradiation. The marked divergence in clinical results of roentgenotherapy in cancer of the breast may be due to differences in reaction of the connective tissue.