

ROENTGEN THERAPY OF EPITHELIOMAS OF THE TONSILLAR REGION, HYPOPHARYNX AND LARYNX FROM 1920 TO 1926*

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I. ANATOMICAL-CLINICAL DEFINITION

AN ADEQUATE clinical observation of cancer, and especially of those cancers which concern us here, implies the necessity of repeated examinations during the course of treatment, as much from the point of view of changes in the appearance of the normal and neoplastic tissues under the influence of radiation as from the point of view of the accuracy of the topographic diagnosis.

When the therapy is used as it is here in cancers that are usually very widespread, the exact diagnosis of the point of origin of the neoplasm is often difficult to establish immediately; it is necessary to await the disappearance of the accompanying inflammation and the progressive diminution of the tumor masses which overrun and mask the initial lesion.

It may happen during the course of a treatment that the topographic diagnosis must be revised. It is found, for example, that extensive cancers beginning in the tonsillar region have been mistaken for cancers of the base of the tongue; that epitheliomas of the mucous membrane of the cheek, maxilla or palate have been mistaken in the beginning for cancers of the tonsillar region. In the same manner a tumor which totally obstructs the laryngeal vestibule is apt to be considered as having originated either in the larynx or pharynx; it is only during the course of treatment that the true primary lesions can be recognized and their true origin established.

The 46 epitheliomas of the tonsillar region which we have treated usually in-

volved the tonsil and the tonsillar pillars, reaching (in more than half of the cases) the palate, the uvula and often the glosso-pharyngeal folds.¹ Frequently they came in contact with the epiglottis; often they extended to the tongue, the mucosa of the cheek, the gingival-jugular folds, the internal aspect of the inferior maxilla; more rarely the involvement reached the pterygo-maxillary region causing trismus. In spite of their large size, they were usually only slightly painful.

The adenopathy, usually early, was constant, large, spherical in form, and somewhat indurated; it often remained movable for a long period over the deep structures. Its site corresponded to the angle of the maxilla; sometimes it descended along the carotid vessels and rarely reached the supraclavicular region; sometimes it was bilateral.

The 89 epitheliomas of the hypopharynx which we have treated, represented very dissimilar types. They originated between the postero-inferior edge of the base of the tongue and the mouth of the esophagus. Those of the superior and lateral edge of the epiglottis, of the lingual aspect of the epiglottis, of the aryteno-, pharyngo- and glosso-epiglottic folds were common. The cancers of the pharyngo-laryngeal canal (or pyriform sinus) and the glosso-epiglottic depressions (or valliculae) have been less numerous. Epitheliomas of the lateral and posterior walls of the pharynx were still less numerous, as were also epitheliomas of the anterior pharyngeal wall, i.e.,

¹ In the Curie Institute, epitheliomas of the tonsillar region of limited extension are treated preferably by radium therapy.

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the pharyngeal mucosa covering the interarytenoid surfaces and the cricoid plate. Epithelioma of the mouth of the esophagus has been rare.

Adenopathies were constantly observed, their site and size varying with the primary location, i.e., either carotid or supraclavicular, and sometimes mastoid. They were frequently infected and in 10 cases they had been removed or incised six months to one year before the diagnosis of their primary origin was established.

The 77 epitheliomas of the larynx which we have treated related especially to the vocal cord, to the subglottic region, to the ventricular band or to the ventricular cavity of Morgagni; they sometimes sprang from the anterior commissure or from the mucosa covering the inferior and laryngeal part of the epiglottis, or from the laryngeal mucosa of the arytenoids, also from the laryngeal slope of the interarytenoid space. These epitheliomas reacted very differently depending upon their point of origin, the degree of infiltration, the invasion of the cartilages and the superimposed infection. Most of these epitheliomas were very extensive and inoperable; others, previously operated upon, recurred; 8 were operable but seemed more amenable to irradiation than surgery.

The epitheliomas of the glottis were not accompanied by adenopathy, which we observed often in epitheliomas affecting the subglottic region. Adenopathies were the rule in epitheliomas of the ventricular bands and cavities, especially when the lesion had broken through the boundaries of the larynx and had assumed the characteristics of cancer of the hypopharynx.

Local recurrence, in case of failure of roentgen therapy, in the type of cancer which we have referred to, manifested itself at any period. It occurred most frequently between the sixth and twelfth months after the beginning of the treatment. In the cases treated between 1920 and 1926, when a patient remained without local signs of disease for fifteen months, we never observed a subsequent recurrence.

In the series of patients treated after 1926, we have observed two local recurrences which manifested themselves only at the end of the third year after the treatment; consequently we believe that a period of control of at least three years is necessary before a local cure can be accepted as probable.

On the other hand, we have observed in some of our patients locally cured, late distant metastases occurring during the third, fourth and fifth years. Therefore a period of control of five years is necessary before a total cure of the cancer process can be considered as probable.

In spite of this, in the attempt to demonstrate the unequal frequency of late metastases in the three varieties of epitheliomas under consideration, we have in Tables I, II and III, given first the results obtained after a period of control of two years. We have also given in the same tables and in the following tables, the statistics of patients living after three, five and eight years, statistics necessarily established on a diminishing number of patients treated.

TABLE I
EPITHELIOMAS OF THE TONSILLAR REGION TREATED
BY X-RAYS 1920-1926

Years	Cases Treated	Locally Cured Two Years after Treatment	Dead after Two Years and Causes of Death	Symptom free at Beginning of 1931
1920	2	0		
1921	5	2		2
1922	3	1		1
1923	3	1	1 Pulmonary metastasis, dead the sixth year after treatment	0
1924	7	1		1
1925	13	1		1
1926	13	6		6
	46	12 (26%)	1	11 in 46 (23%)

II. STATISTICS AND CLASSIFICATION
 OF RESULTS

I. Tables I, II, III and IV show that 212 patients have been treated completely or have begun treatment by roentgen rays in my service at the Curie Institute from 1920 to 1926; 157 (74 per cent) died during the first two years following the treatment,

These tables show, in addition, that the proportion of locally cured patients is essentially comparable in the three groups of epitheliomas under consideration, i.e.:

12 out of 46 (26 per cent) for cancers of the tonsillar region.

18 out of 89 (20 per cent) for cancers of the hypopharynx.

TABLE II
 EPITHELIOMAS OF THE LOWER PHARYNX TREATED BY X-RAYS 1920-1926

Years	Cases Treated	Locally Cured Two Years After Treatment	Dead After Two Years and Causes of Death	Symptom-free at Beginning of 1931
1920				
1921	7	1	1 Pulmonary metastasis, dead the sixth year after treatment	0
1922	11	4	3 (1) Prostatic hypertrophy, dead the fourth year after treatment; (2 and 3) Mediastinal and hepatic metastasis, dead the fifth year after treatment	1
1923	8	2	1 Abdominal metastasis, dead at beginning of the third year after treatment	1
1924	19	1		1
1925	24	5	2 Pulmonary and mediastinal metastasis, dead the third year after treatment	3
1926	20	5	2 Abdominal metastasis, dead the third year after treatment	3
	89	18 (20%)	9	9 in 89 (10%)
			8 in 18 (44%) dead of late metastasis 1 dead of intercurrent disease	

either from extension of the primary lesion, or from early metastasis, sometimes from local or general post-roentgen accidents, and 55 (26 per cent) have been cured of the primary cancerous lesion.

25 out of 77 (32 per cent) for cancers of the larynx.

None of these patients have presented local recurrence, but the proportion of late metastases occurring more than two years

TABLE III
EPITHELIOMAS OF THE LARYNX TREATED BY X-RAYS 1920-1926

Years	Cases Treated	Locally Cured Two Years after Treatment	Dead after Two Years and Causes of Death	Symptom-free at Beginning of 1931
1920				
1921	8	4		4
1922	11	1	1 Cardiac accidents, dead the fourth year after treatment	0
1923	12	2		2
1924	12	3	2 (1) Tuberculosis, dead the third year after treatment (2) Thoracic metastasis, dead the third year after treatment	1
1925	17	6		6
1926	17	9		9
	77	25 (32%)	3	22 (28%)

TABLE IV
EPITHELIOMAS OF THE TONSILLAR REGION, HYPOPHARYNX AND LARYNX TREATED BY X-RAYS 1920-1926
Proportion of Thoracic or Abdominal Metastasis After More Than Two Years of Local Cure

	Cases Treated	Locally Cured Two Years after Treatment	Symptom-free at Beginning of 1931	Causes of Death after More Than Two Years	
				Intercurrent diseases	Thoracic or abdominal metastasis
Tonsillar region	46	12 (26%)	11 in 46 (23%)		1 in 12 (8%)
Hypopharynx	89	18 (20%)	9 in 89 (10%)	(1) Prostatic hypertrophy	8 in 18 (44%)
Larynx	77	25 (32%)	22 in 77 (28%)	(1) Tuberculosis (1) Cardiac accidents	1 in 25 (4%)
	212	55 (26%)	42 in 212 (20%)	3	10 in 55 (18%)

after treatment varies with the location:

1 out of 12 (8 per cent) for cancers of the tonsillar region.

8 out of 18 (44 per cent) for cancers of the hypopharynx.

1 out of 25 (4 per cent) for cancers of the larynx;

so that the proportion of those living after three years of control remains for the first and third group:

12 out of 46 (26 per cent);

25 out of 77 (32 per cent);

but the percentage diminishes in epitheliomas of the hypopharynx to:

13 out of 89 (14 per cent).

We have seen only one case of late pulmonary metastasis occurring during the sixth year after treatment in our epitheliomas of the tonsillar region, and one case of metastasis during the fourth year in our epitheliomas of the larynx. In spite of the constancy of glandular invasion in epithelioma of the tonsillar region and in spite of their large size, late distant metastasis, contrary to what one would expect, seemed little to be feared in this type of cancer.

In epitheliomas of the hypopharynx, out

tion of definite cures was 24 per cent (37 out of 149). This difference in results can be attributed partly to a variable proportion of favorable cases during these years (1921, for example), and partly to more or less marked differences in technique during the period of study which represented the first seven years.

3. Table VI shows that the permanence of percentage of results considered in consecutive years, differs depending upon the location of the lesion. In epitheliomas of the hypopharynx, the percentage of cures

TABLE V

EPITHELIOMAS OF THE TONSILLAR REGION, HYPOPHARYNX AND LARYNX TREATED BY X-RAYS 1920-1926
Proportion of Survivals, by Years, at Beginning of 1931

Years	Cases Treated	Symptom-free at Beginning of 1931				Survival Period
		Tonsillar Region	Hypopharynx	Larynx	Total	
1920	2	0 out of 2			0	
1921	20	2 out of 5	0 out of 7	4 out of 8	6 (30%)	9 years
1922	25	1 out of 3	1 out of 11	0 out of 11	2 (8%)	8 years
1923	23	0 out of 3	1 out of 8	2 out of 12	3 (13%)	7 years
1924	38	1 out of 7	1 out of 19	1 out of 12	3 (8%)	6 years
1925	54	1 out of 13	1 out of 24	6 out of 17	10 (18%)	5 years
1926	50	6 out of 13	3 out of 20	9 out of 17	18 (36%)	4 years
	212	23%	10%	28%	42(20%)	4 to 9 years

of 18 patients locally cured after two years, we have observed 8 cases of late metastasis (3 abdominal and 2 thoracic during the third year, 2 thoracic during the fifth year, 1 pulmonary during the sixth year). The results of treatment of epitheliomas of the hypopharynx, although as favorable from the standpoint of local cure as for epitheliomas of the tonsillar region and larynx, are uncertain because of the development of metastasis.

2. It can be seen from Table v that the results controlled to January, 1931, for treatments given during the period of seven years (from 1920 to 1926) have varied according to the years. In 1922 and 1924, the proportion of favorable results was very low—only 8 per cent of definite cures—whereas for the other five years the propor-

tion decreases progressively and falls to 0 after nine years. In epitheliomas of the tonsillar region and larynx, the percentage of cures is maintained in a relatively constant manner, regardless of whether the observation is made after two, six or nine years.

In this table it may be seen that the proportion of cures controlled three years after treatment in the patients treated from 1920 to 1926, is 50 out of 212 (23 per cent). These can be divided as follows:

12 out of 46 (26 per cent) for epitheliomas of the tonsillar region.

13 out of 89 (14 per cent) for epitheliomas of the hypopharynx.

25 out of 77 (32 per cent) for epitheliomas of the larynx.

The proportion of cures controlled five years after treatment in the patients

TABLE VI
EPITHELIOMAS OF THE TONSILLAR REGION, HYPOPHARYNX AND LARYNX TREATED BY X-RAYS 1920-1926
Results of Roentgen Therapy at Beginning of 1931 After More Than:

	Two Years (Cases Treated 1920-1926)	Three Years (Cases Treated 1920-1926)	Four Years (Cases Treated 1920-1926)	Five Years (Cases Treated 1920-1925)	Six Years (Cases Treated 1920-1924)	Seven Years (Cases Treated 1920-1923)	Eight Years (Cases Treated 1920-1922)	Nine Years (Cases Treated 1920-1921)
Tonsillar region	12 in 46 (26%)	12 in 46 (26%)	12 in 46 (26%)	6 in 33 (18%)	5 in 20 (25%)	3 in 13 (23%)	3 in 10 (30%)	2 in 7 (28%)
Hypo- pharynx	18 in 89 (20%)	13 in 89 (14%)	12 in 89 (13%)	7 in 69 (10%)	4 in 45 (9%)	2 in 26 (7%)	1 in 18 (5%)	0 in 7
Larynx	25 in 77 (32%)	25 in 77 (32%)	22 in 77 (28%)	13 in 60 (21%)	7 in 43 (16%)	6 in 31 (19%)	4 in 19 (21%)	4 in 8 (50%)
	55 in 212 (26%)	50 in 212 (23%)	46 in 212 (21%)	26 in 162 (16%)	16 in 108 (14%)	11 in 70 (16%)	8 in 47 (17%)	6 in 22 (27%)

treated from 1920 to 1925 is 27 out of 162 (16 per cent), which may be divided as follows:

6 out of 33 (18 per cent) for epitheliomas of the tonsillar region.

8 out of 69 (11 per cent) for epitheliomas of the hypopharynx.

13 out of 60 (21 per cent) for epitheliomas of the larynx.

The proportion of cures controlled eight years after treatment in the patients treated from 1920 to 1922 is 8 out of 47 (17 per cent) which can be divided as follows:

3 out of 10 (30 per cent) for epitheliomas of the tonsillar region.

1 out of 18 (5 per cent) for epitheliomas of the hypopharynx.

4 out of 19 (21 per cent) for epitheliomas of the larynx.

4. Table VII shows that the proportion of females with epithelioma of the tonsillar region, hypopharynx and larynx, is small compared with the proportion of males affected by these lesions: out of 212 cases treated, 197 were males (93 per cent), and 15 were females (7 per cent). This table also shows that the cure of these epitheliomas is more easily accomplished in women

than in men, since up to January 1, 1931, out of 15 women treated, 9 (60 per cent) are free of disease from four to nine years, whereas the proportion of men treated during the same period and free of symptoms at the same time (1931) is only 33 out of 197 (16 per cent).

TABLE VII
EPITHELIOMAS OF THE TONSILLAR REGION, HYPOPHARYNX AND LARYNX TREATED BY X-RAYS
1920-1926
Proportion of Survivals at Beginning of 1931, in Males and Females

	Cases Treated	Symptom-free at Beginning of 1931
Males	197 (93%)	33 (16%)
Females	15 (7%)	9 (60%)
	212	42 (20%)

5. Critique of Results. The epitheliomas of the tonsillar region, in spite of the very extensive development of the lesions in the primary growth and the invasion of lymphatic glands, have given us fairly good results during the years 1921 to 1926. But it is only since 1926 that the results of roentgen therapy alone have shown an appreciable improvement (46 per cent).

The cancers of the hypopharynx which we have treated were all inoperable; therefore none of those which were cured locally had been subjected to previous surgical intervention.

Among the epitheliomas of the larynx there were a variety situated in the cord, glottis or even subglottis, sometimes small, at other times reaching a considerable size; but in all instances they infiltrated the laryngeal muscles only slightly, leaving the organ fairly mobile. These epitheliomas are easily cured by irradiation and offer almost constant success to roentgen therapy. Surgery is also successful in a high proportion of this variety, but the conservation of the voice is less perfect after surgery than after radiotherapy. On the other hand, when roentgen therapy given in curative doses fails, future surgical intervention is rendered dangerous on account of the changes provoked in the tissues, while irradiation can be used without danger in a postoperative recurrence. The satisfactory results obtained in 1921 can be explained partly by the fact that in two patients with epithelioma of the cord without infiltration and without diminution of mobility of the larynx, there were contraindications to operation, one because the lesions were bilateral, having spread from the anterior commissure to the arytenoids, the other on account of obesity.

On the contrary, when a very small cancer of the vocal cord has caused fixation by infiltration of the muscles and if it has already reached the cartilages or provoked a perichondritis, and when histological examination shows a particularly resistant epithelioma, failure of roentgen therapy is the rule. If in such cases, as Hautant has practised several times, a resection of the infiltrated and infected areas adherent to the cartilage is performed (without pretending that the operative procedure removes the entire neoplasm) roentgen therapy can effect a definite disappearance of the neoplastic process. In several cases of cancer of the larynx treated in 1926, this combination of surgery and radiation was

used, the result of which has been cure in 53 per cent.

Among the cases treated, there exists a certain number in which the site of origin is not in the vocal cord, but in the ventricular band. In epitheliomas of the band, although showing a marked degree of infiltration and infection and involvement of the cartilage, the histological form is generally much more favorable and roentgen therapy can effect a cure without recourse to surgery, which in tumors of marked radiosensitivity but equally marked tendency to diffusion, is apt to facilitate the dissemination of neoplastic cells.

Considering the large number of varieties and locations of epitheliomas of the hypopharynx and larynx, it is very difficult to decide which therapeutic method is to be applied. But it may be stated at present that for certain locations and certain states of development, roentgen therapy should accomplish almost unvarying success, whereas for other locations and other states of development, roentgen therapy, at least at present, yields no results. There are cases in which the association of surgery and irradiation or irradiation and surgery should be advantageous, but the rules for the selection of these cases are not definite.

The presence of very extensive adenopathy, sometimes subclavicular and retroclavicular, frequently infected and often bilateral, adds to the complexity of the problem. At any rate, the cure of unilateral adenopathy by roentgen therapy is relatively easy except in the cases where the lymphatic glands are the seat of an associated bacterial infection.

III. TECHNIQUE OF TREATMENT

I. Total doses. Total duration of treatment. Number and surface area of fields. Focal distance.

The epitheliomas of the tonsillar region in females which have been cured (4 out of 8 cases treated) have received cutaneous doses of 50, 69, 73 and 78 Holzkecht units (H), i.e., 5,000 r, 6,900 r, 7,300 r, and 7,800

r (International unit)² administered consecutively over periods of 17, 20, 41 and 29 days. In the cured males, the treatments have been 68, 78, 79 and 79 H, administered over periods of 37, 30, 34 and 40 days. In 3 other cases of cured males, very weak doses of roentgen rays (40 H in 14 days, 59 H in 83 days and 59 H in 50 days) had been supplemented with radium.

Doses of 100 to 120 H were frequently administered in 1923; we reached 150 and 160 H in 40 to 45 days during the year 1924; in 1926, we reached doses of 100 to 130 H in 30 to 50 days. These treatments with high doses did not give us any favorable results, except for one patient who, in 1923, received 150 H in 41 days, and was cured locally. During the fifth year, however, he developed radionecrosis of the inferior maxilla which culminated in elimination of a sequestrum followed by cicatrization. Some time later extensive pulmonary metastases appeared which caused death six years after treatment.

In all these cases, up to 1923, the fields have been 50 to 100 sq. cm.; later they were increased to 150 and even 200 sq. cm.; the focal distance has been from 40 to 50 cm.

The epitheliomas of the hypopharynx in females, cured in a proportion of 2 out of 4, have received in one case 46 H in 8 days with a field of 60 sq. cm., in the other case 77 H was administered in 30 days, with a slightly larger field.

In the males, the doses which have resulted in cures have been 60 H in 10 days, 66 H in 24 days, 71 H in 31 days, 75 H in 25 and 32 days; in 2 other cured cases, the doses were administered over very long periods: 74 H in 61 days and 81 H in 47 days. Treatment has been attempted with doses of 90, 100 and 105 H with no favorable results. The fields which until 1923 had been

less than 100 sq. cm. were subsequently increased to 150 and 200 sq. cm.

The epitheliomas of the larynx in females (3 cases cured out of 3 cases treated) received 49 H in 9 days, 54 H in 16 days, and 80 H in 29 days.

In males, we have 19 cured cases, of which 5 were treated during a period of less than 15 days. One patient received 60 H in 8 days; 2 others received 68 and 85 H in 11 days; 2 others 56 and 66 H in 12 days. Eleven patients cured were treated over a period of between 15 and 21 days, with doses averaging between 65 and 71 H. Three patients were cured by treatment extending over a period longer than 21 days: one patient received 71 H in 26 days, another 77 H in 28 days, and a third 75 H in 39 days. A certain number of patients have been treated with 90 and 100 H, but yielded no favorable results.

Up to 1924, the fields were less than 100 sq. cm.; since then they have been increased to 130 sq. cm.

The number of fields or portals of entry has varied between 2 and 4. In cancers of the tonsillar region and lower pharynx, we have usually employed 3 fields on the side of the lesion and one field on the opposite side. Of these 4 fields, the two lateral fields were parallel and crossed by the transverse beams, the three fields on the side of the lesion having overlapping edges. Of the three unilateral fields, the anterior and the posterior were traversed by a sagittal beam, i.e., anteroposterior for one of the fields, and posteroanterior for the other. In this manner, we reduced the useless energy absorbed by the deep tissues, as well as the general accidents which result from it.

In cancer of the larynx, 2 fields have usually been employed, lateral and symmetrical, traversed by transverse beams; an anterior field traversed by an anteroposterior beam has occasionally been utilized.

From the mass of facts which have been cited here, the following conclusions may be drawn:

(a) The cutaneous doses which have yielded cures in the three groups of cancer

² We have adopted the equivalent of 100 r for 1 H. While this equivalent is convenient it is not absolutely exact. When the field is very small, i.e., when there is a tendency toward the suppression of the secondary rays, 1 H seems to be less than 100 r; if the field reaches large dimensions (300 to 400 sq. cm.) 1 H corresponds to more than 100 r.

have been essentially similar, in spite of the variations in the extent of the lesions, in the surface area and number of fields and in the focal distance. In males, the doses have varied between 65 and 80 H (6,500 to 8,000 r); they have been lower in general for cancer of the larynx and higher for the two other varieties.

(b) The increase of dosage above 80 H has not given favorable results, i.e., cures; in the same way, diminution of the doses below 65 H has yielded cures only in women or in cases in which the neck was small.

(c) The dose which proved efficacious in the epitheliomas treated seemed approximately the same regardless of the duration of the treatment.

(d) The average duration of treatment in the cured males has been 30 to 40 days for the tonsillar region; 24 to 31 days for the lower pharynx and 15 to 21 days for the larynx.

The above conclusions lead to the following considerations:

In proportioning the surface area of the fields to the extent of the lesions and to their depth, we have been led to employ larger surface areas for cancers of the tonsillar region and lower pharynx than for cancers of the larynx. In fact, cancer of the two former locations is deeper and more extensive than laryngeal cancer, and as a rule presents adenopathies by which the epitheliomas of the larynx are rarely accompanied. Thus a patient irradiated through a small field can receive the dose necessary for cure of the neoplasm in a short time, without grave accidents, general or local. A patient irradiated through a large field cannot receive the same dose in as short a time without suffering ill effects. That is why the time of treatment is found considerably increased for the two former groups of cancers (tonsillar region and hypopharynx), whereas it is much shorter for cancer of the larynx. At any rate, it is noteworthy that cancers of the larynx, which are generally the most radioresistant of all the cancers which we

have described here, have benefited from the shortest treatments. The conclusion is therefore reached that in epitheliomas whose degree of radiosensitivity is not very different from the varieties of pavement epitheliomas, which we can hope to cure actually, it seems wise to depend upon the dimensions of the neoplasm in deciding upon the duration of the treatment: a very small lesion can be treated in the short time of about 15 days; a lesion of medium size in 20 to 25 days, a very large lesion with large adenopathy in 35 to 40 days; it is altogether impossible to do otherwise in the latter case.

2. *Conduct of treatment. Duration of irradiation. Rapidity of the regression of the neoplasm and of recurrences.*

The continuity of treatment, according to the ideas and experiments of Regaud, has always been respected at all times. When the total duration of treatment has been less than 20 days, the treatment has always been uninterrupted, usually giving two irradiations daily. When the duration of treatment reached 25 days, there were sometimes several days of rest, necessitated by the extreme fatigue of the patient resulting from the use of larger fields. When the duration reached 30 to 40 days, the treatment was either continuous, or more often divided into two or three series of which the first was the most important, the total treatment remaining unified and complete.

In the unsuccessful cases, in which supplementary treatments were attempted, about two to four weeks after the cessation of the first, the results have not been good. Neither has a second complete treatment given good results save in exceptional cases. Among the 55 patients cured locally, 2 patients owe their local cure to a second treatment with roentgen rays given six to seven months after the first.

The average total duration of irradiation has been 25 to 35 hours; the daily dose has varied between 2 H (200 r) per day and 9 H (900 r) per day. The duration of the daily

irradiation has been about 50 minutes in the first case, which gives an hourly intensity of 2.40; it lasted 3 to 4 hours in two daily seances in the second case, which gives an hourly intensity reaching 2.25 to 3; this hourly intensity seems to us not to be excessive.

The neoplastic regression and the disappearance of the glandular masses have been effected after the diverse treatments at irregular intervals. The rapidity of the disappearance of the neoplasm has been the result of numerous factors. Among the most important are: the histological type, the degree of infiltration, the degree of infection and the duration of the treatment.

For the doses indicated, with treatments of 8 to 15 days, the rapidity of the disappearance of the neoplastic lesions has been very marked; after the end of treatment, or at most after 25 days, the neoplasm was no longer appreciable.

In cases in which the epitheliomas definitely disappeared, the result at first seemed excellent, but in these cases we have observed besides sclerodermas and some painful myoscleroses, partial chondro-necroses with elimination of small fragments of cartilage, and also in one case, osteo-radionecrosis of the inferior maxilla which caused death twenty-one months after treatment.³

In those cases in which a cure was not obtained, the condition of the patient was aggravated by the treatment given during a short period. Five to six months after treatment one could observe the appearance of multiple edema at the level and in the neighborhood of the irradiated zones. Following this edema, zones of radionecrosis, with very extensive infection appeared in the mucous membrane. Within the sloughing zones the neoplastic development be-

came more rapid and more painful than before the treatment.

Treatment over long periods, from 30 to 35 days, for example, has sometimes led us to fear non-sterilization of the tumor, either during or after the treatment, because the regression of the tumor was sometimes incomplete two months after the beginning of irradiation. In the cured cases, the general condition of the patient was changed before the disappearance of the tumor. In those cases which were not cured, we found neither edema nor zones of radionecrotic destruction; the neoplastic evolution appeared neither more painful nor more rapid than before the treatment; the survival was almost always longer than in the cases which were treated over short periods.

In summary, the lengthening of the duration of treatment has seemed to diminish the number of cures, but has seemed to diminish the rapidity of development of recurrences. On the other hand, the shortening of the duration of treatment has seemed to increase the number of cures, but has seemed to accelerate the rapidity of evolution of recurrences.

3. *Physical conditions of treatment. Physical and biological estimation of doses.*

The tension used at the poles of the roentgen tubes was 130 to 140 kv. in 1920 and 1921, with a filtration of 10, 12 and 14 mm. Al. In 1922, the tension was raised to 175 kv., with 1 mm. Zn, then 1.5 mm. Zn; finally it remained between 175 and 190 kv. for filtrations of 2 mm. Zn plus 3 mm. Al and 1 cm. of wood against the secondary rays from the zinc. In the beginning, the intensity of the current traversing the tubes was 2.5 to 3 ma., until 1921, then from 4 to 5 ma. after 1922. The focal skin distance, first limited to 35 to 40 cm., was increased to 45 to 50 cm. after 1923.

The quantity of roentgen rays has been measured at the skin by means of ionometric apparatus (Solomon, Dauvillier, Bruzeau, Ferroux), or by means of the colorimetric scale of Holzknacht, with disks of platino-cyanide of barium selected and controlled as perfectly as possible.

³ Among the patients treated in 1927, over short periods, we have seen 2 other cases of osteonecrotic accidents at the level of the inferior maxilla, which caused death two and a half years after the cure. The treatments had been given in 11 and 15 days. We have therefore abandoned these treatments over short periods, except for very small lesions and in particular cases: the endolaryngeal cancers are not treated in less than 15 days; those of the hypopharynx and tonsillar region in not less than 20 days.

The physical conditions and the biological effects were always exactly noted. In this way the measured dose could be evaluated according to the physical constants and in a certain measure controlled by the biological findings.

The precise biological effects are determined under the following physical conditions: focal distance, 50 cm.; field 50 sq. cm.; 4 ma.; 175 kv.; filter, 2 mm. Zn; generators, constant potential of Gaiffe or Veifa Werke apparatus with condensers.

One dose of 45 to 50 H (4,500 to 5,000 r) distributed over ten days in two daily sittings of one hour each or 20 hours, over the same lateral surface of the neck causes at the 26th to the 28th day a cutaneous lesion characterized by a loss of all the epithelial layers with denudation of the dermis; the lesion should be repaired after 15 days, i.e., about the 40th to the 42nd day, without leaving any visible trace; this is the "radioepidermitis" of Regaud and Nogier. If the dose has been greater, the time necessary for the skin recovery is longer; if the dose has been weaker, the time necessary for the recovery of the skin is shorter, as we will show below. The time of evolution of the epidermal lesion can constitute in itself a biological control of the dose.

IV. GOVERNING IDEAS IN THE CONDUCT OF TREATMENT

1. *Production of epithelial radiolesions in the course of treatments given during 1920 to 1926.*

The 42 patients irradiated during the years 1920 to 1926 for epitheliomas of the tonsillar region, hypopharynx and larynx, and actually entirely free of symptoms of cancer have all been treated by the method which we call "epidermicide"; all have presented a "radioepithelitis" of the mucosa and a cutaneous "radioepidermitis." The duration of evolution of the radiolesions was always about thirteen to fifteen days. In the course of these seven years, we have sometimes attempted to reduce the intensity and duration of evolution of the epi-

thelial radiolesions, especially of the radioepithelitis of the mucous membrane. The evolution of this reaction was reduced to ten days and sometimes even to five days; in this manner we spare the patient the pain of the radioepithelitis which is sometimes very marked during movements of deglutition. A recurrence always resulted from this method of treatment.

"Radioepidermitis" and "Radioepithelitis." An observation of the facts leads us to admit that the radiosensitivity of cancer cells of epidermal origin is usually of the same degree as the radiosensitivity of the germinal cells of the epidermis. If one can effect the complete destruction of the germinal cells of the epidermis of the irradiated surface without seriously injuring the dermis, an epidermal cancer of small volume, situated in the same plane in the center of the irradiated surface can also be destroyed. Daily experiences have demonstrated the truth of this elementary principle. Thus, the radioepidermitis that Regaud and Nogier have observed and described in 1913, is characterized by the total destruction of the cells of the germinal layer of the epidermis with denudation of the nearly normal dermis.

The repair of the radioepidermitis occurs from the periphery toward the center, by proliferation of the peripheral epithelial cells, situated along the border of the field, and their development assumes a typical polycyclic appearance, while the derma is slightly modified or not altered at all (Figs. 1 and 2). When the derma has been markedly changed, the repair is effected by proliferation of the peripheral epithelial cells whose development assumes a linear form (Figs. 3 and 4). If not all the squamous epithelial cells in the irradiated field are destroyed, the repair occurs partly from the periphery and partly from the central islands arising from the squamous epithelial cells of the lumina of the sweat glands and of the sebaceous glands (Fig. 5).

In the physical conditions of treatment which we have already indicated, the radioepidermitis appears about the 26th to 28th



FIG. 1. "Radioepidermitis" with derma slightly modified. The proliferation of the peripheral epithelial cells, situated along the border of the field, assumes a typical polycyclic appearance.

day after the beginning of the treatment; it returns to normal in thirteen to fifteen days and terminates at about the 40th to 42nd day, generally leaving no visible sign on the skin surface. The radioepithelitis of the mucosa, or the total destruction of the germinal cells of the epithelium of the mucosa, with denudation of the dermis followed by the formation of plates of false membrane that are more or less thick, appears in the layer of the mucosa at an earlier date, thirteen to fourteen days after the beginning of the irradiation. The duration of its evolution is also about two weeks. At about the 26th to 28th day the radioepithelitis is repaired, leaving not a single trace in the layer of the mucosa. Thus the radioepithelitis completes its evolution at the moment when the radioepidermitis appears, so that the whole of the duration of the irradiation, of the radioepithelitis

and of the radioepidermitis will constitute a series of three consecutive periods of about two weeks each, or six weeks (Table VIII, I).

In order to obtain a typical radioepithelitis, it is necessary that the mucosa receive a dose equal to 35 H. If the patient's neck is of small dimensions, one can obtain a radioepithelitis under the conditions indicated above, i.e., when the skin has received 45 to 50 H through a single portal of entry. These cases are exceptional. When the patient's neck is of medium size, in order to obtain the desired reaction in the mucosa one should employ two portals of entry, opposite one another, in order to administer a total cutaneous dose of at least 60 H. This is what we have wished to show in Table VIII when we indicate 45 H through one portal of entry and 15 H through the opposite field.

When the periods of evolution of the two radiolesions overlap (Table VIII, II), i.e.,



FIG. 2 "Radioepidermitis" with derma more modified.

when the radioepithelitis repairs itself only after the 30th, 35th, 40th day, or even later, and when the radioepidermitis appears before the 24th day, even the 20th day, it is because the division of the irradiation has been incorrect, because the doses have been too large, or because the time of the treatment has been too short for the size of the field used.

When the periods of evolution of the two radiolesions are definitely separated, when the radioepithelitis is repaired early, on the 26th, 24th or even 22nd day, and the radioepidermitis does not appear until the 30th or 32nd day (Table VIII, III), it is again because the division of the irradiations has been incorrect; either the doses were too weak or the periods of treatment were too long for the field employed.

Under these circumstances, the radioepithelitis and radioepidermitis repair in five to ten days and there is great possi-



FIG. 4. The repair is very slow. The proliferation of the peripheral cells assumes a linear form.



FIG. 3. "Radioepidermitis" with derma greatly modified.

bility that a cancericidal effect, at the site of the primary lesion and of the lymphatic glands, has not been produced.

The duration of the evolution of the radiolesions thus constitutes a sufficiently exact control of the phenomena obtained at the end of the irradiations and consequently a control of the correct division of a treatment. But the conditions of treatment described above are appropriate only for a small lesion and for a small field, which renders a short treatment possible; it is a scheme of minimum duration of treatment. It can be considered as a typical treatment of a very small non-infiltrating epithelioma of the larynx that is not adherent to the cartilage.

The conditions are necessarily different when the lesions are more extensive, necessitating the use of larger fields and consequently longer periods of treatment.

These therapeutic indications can only be very incomplete because, besides the

small variations in the time of appearance of the radiolesions of the mucosa in general, and in the duration of their evolution in different individuals irradiated under identical conditions, one can observe in the same individual on the surface of different segments of the mucosa, the radioepithelitis occurring at different times.

The different times of appearance of the radioepithelitis are caused by the notable differences in the cellular types which cover



FIG. 5. The repair assumes on the anterior border a polycyclic appearance, on the posterior border a linear form, and takes place partly from the periphery and partly from the central islands.

the segments considered. They can be produced by variations in the daily division of doses, duration of irradiation and total duration of the treatment.

In general, the most radiosensitive of all the mucous membranes, that in which the radioepithelitis appears first, is the mucosa at the union of the pillars and the uvula. Under the conditions stated, it becomes

covered by false membranes on the 13th day, one day before the posterior wall of the hypopharynx; the vallecular regions, the origin of the pharyngo-laryngeal furrows and the floor of the mouth have their reaction somewhat later. The mucous membranes which cover the cheeks, the horizontal and vertical branches of the inferior maxilla, become covered by false membranes about the 16th day, and their radioepithelitis demands slightly higher doses. The laryngeal surface of the epiglottis, the laryngeal part of the interarytenoid space, and the base of the tongue, are not covered by false membranes until about the 18th day. The vocal cords, the dorsal and anterior surfaces of the tongue do not become covered with false membranes until the 20th day; sometimes the 22nd day, and in response to higher and higher doses.

The differences in the dates of appearance of the radioepithelitis for the different segments of irradiated mucous membranes throw some light on the difference in radiosensitivity of different segments of mucosa; they correspond roughly to the same difference in the radiosensitivity of epitheliomas developed in the areas of these diverse segments. These are the indications that are sometimes of importance in the choice of duration of the treatments.

2. *Doses and cancericidal effects.* To sum up, if the field is small and if the distribution of irradiation is accomplished in the maximum period of fifteen days, we consider that the doses capable of provoking the destruction of epithelial cells correspond, for the skin, to 45 H (about 4,500 r); for the mucous membranes to 35 H (about 3,500 r). The doses necessary for the destruction of epitheliomas whose radiosensitivity is similar to that of cutaneous epithelium should reach 45 H (about 4,500 r). The dose necessary for the destruction of epitheliomas whose sensitivity is analogous to the epithelial cells of the mucous membranes is about 35 H (3,500 r). These doses which should necessarily be modified according to intervening infection, deep in-

filtration, or adherence to the cartilages, have permitted us to cure some cancers more easily because of their greater radiosensitivity. In order to attain these doses in the area of the lesion to be destroyed, we have been obliged to utilize, for the combined portals of entry, a total dose nearly double the preceding one.

We have seen that in the treatment of

trary, aggravation of the patient's condition and increased rapidity of recurrence have been the rule.

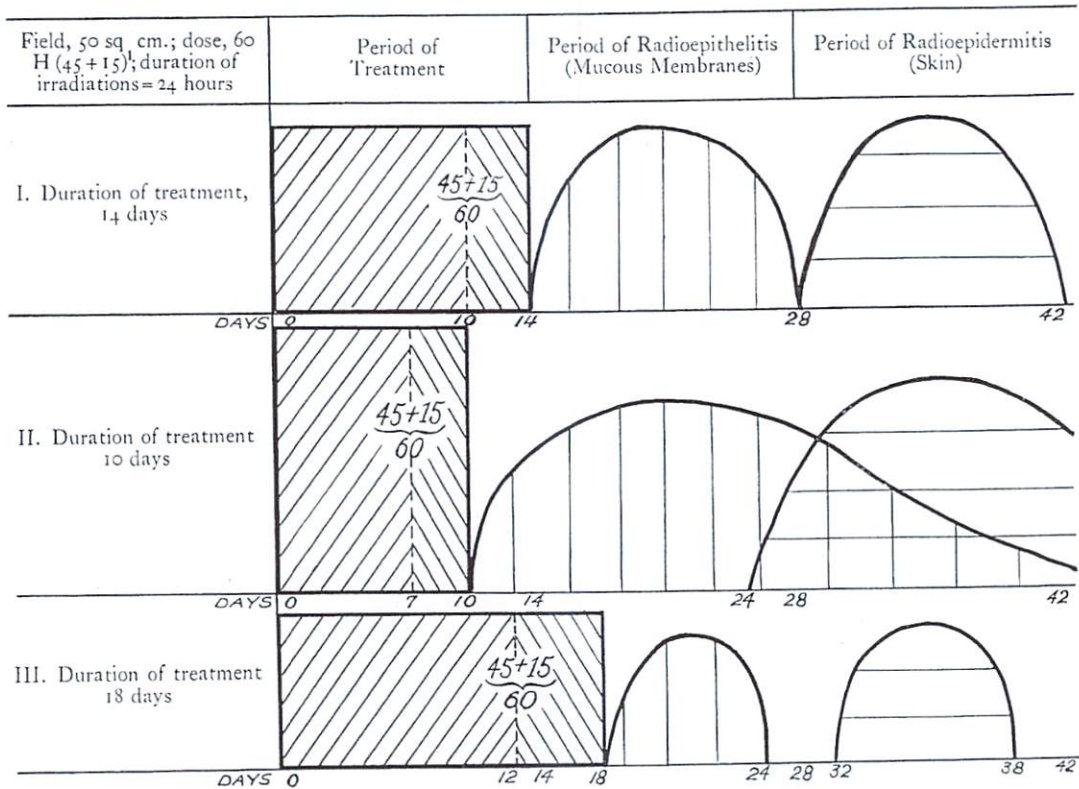
Under the conditions in which our treatments were conducted, the cancericidal effects did not increase proportionately with the doses, beyond a certain value.

Neither do the cancericidal effects increase proportionately with the time of

TABLE VIII

FIGURES ILLUSTRATING THE EVOLUTION OF MUCOUS MEMBRANE AND CUTANEOUS LESIONS OF THE NORMAL EPITHELIUM IN ROENTGEN THERAPY OF SQUAMOUS EPITHELIOMAS OF THE HYPOPHARYNX AND LARYNX.

The Whole is Composed of Three Equal Periods of Two Weeks Each or Six Weeks.



¹ 45 H is given to one side of the neck; 15 H to the other side.

pavement epitheliomas there is no relation, up to a certain limit, between the doses received and the frequency of cures, regardless of the degree of radiosensitivity. Our patients have been cured with doses between 7,000 and 8,000 r, or 70 to 80 H. When the doses have reached 90, 100, 120 and 150 H, there was no cure; on the con-

treatment—quite the contrary. The real or apparent loss of radiosensitivity (immunization) of the cells of squamous epithelioma is often appreciable about the 30th day after the beginning of the treatment. In the same way, the epithelial radiolesions of the skin and mucous membranes are more difficult to provoke (even when

the doses are slightly increased) the longer the treatments have lasted.

V. COMPLICATIONS AND ACCIDENTS

The complications and accidents observed during the course of our treatments have been due, on the one hand, to connective tissue vascular lesions and, on the other hand, to toxic phenomena in which the chemical transformations of the connective tissue probably play a part.

The caustic or semi-caustic methods have often yielded cures of small superficial epitheliomas or of those situated in a particularly tolerant zone. The connective-vascular tissue was greatly modified at the same time that the epithelioma was destroyed. When one deals with cancers located in the larynx, mouth and pharynx, a more selective method (cytocaustic electricity of Regaud) must be employed in order to protect the tissues surrounding the neoplasm. With roentgen rays we have not obtained cures of epitheliomas in these locations in treatments of less than eight days.

When the epithelioma is further developed and more deeply situated in the cervical region, and when more extensive fields are employed, the necessity of protecting the connective tissues becomes more and more important, and this fact necessitates a prolongation of the time of the treatment, for the post-roentgen complications always take on a graver aspect as the total duration of treatment is shorter and the number of hours of irradiation is less.

The complications which we have observed have been local or general, immediate or late.

1. *Immediate local complications.* The first of all the complications is characterized by the appearance of a precocious edema. The precocious edemas are glandular, appearing in the region of the parotid, submaxillary and sublingual glands; they are also subcutaneous. They often appear at the beginning of the irradiation, disappearing after about twenty hours and re-appearing during the second irradiation; some-

times they are slight, sometimes they become chronic during the course of treatment, leaving characteristic changes in the appearance of the chin and face.

The precocious edemas also occur in the deeper tissues and are to be seen in the mucous membranes at the same time that they are visible in the neoplasm itself. In the cancers of the larynx and hypopharynx, if edema appears before the neoplasm has regressed, it provokes dyspneic accidents which necessitate tracheotomy.

Parallel with the edemas, there frequently appear intense and early cutaneous erythemas accompanied by enantheas of the mucous membranes.

The importance of these edemas, erythemas, enantheas and their extent, the intensity of the pain which accompanies them and their tendency to chronicity, vary with the size of the fields, the hourly and daily intensities, the daily and total doses, and the previous state of the capillaries. When they are very intense and early, the edemas and erythemas constitute proof of disturbances in the subcutaneous and submucous blood capillaries. They seem to modify unfavorably the radiosensitivity of the epitheliomas and their adenopathies; they are also an important factor in the appearance of late complications.

Sometimes the treatments have caused more or less important early hemorrhages following the sudden melting of the neoplastic masses, due to the local congestion secondary to the irradiation. They have also occasioned the development of inflamed glands with elevation of temperature and acute perichondritis; not only have these accidents been serious in themselves, but they have nearly always necessitated the abandonment of treatment, thus leading to failure.

There exists a series of early local complications, difficult to avoid, but much less grave. They are: dryness of the mucous membranes of the mouth and pharynx, with thickening of the saliva; perversion or complete loss of taste due to modification

or diminution of glandular secretions; dysphagia, which precedes the radioepithelitis of the mucous membranes; the radioepithelitis of the mucous membranes themselves, a complication still inevitable because when we have wished to reduce or suppress it, we have been unable to effect a cure; finally the cutaneous radioepidermitis which as far as we can see, constitutes a complication only when its restoration is late.

From time to time during the course of treatment, we have encountered myoclonic crises in the muscles of the neck, arms and trunk, and paresis of the arms and legs which have never lasted more than one or two months.

2. *Late local complications.* These have been the result of the tendency to chronicity of the complications indicated above: the persistence of the dryness of the mucous membranes and of the perversion of taste lasting sometimes as long as one or two years; the chronic edemas constantly becoming harder and thicker and developing into a scleroderma; in certain cases we found cutaneous atrophy with discoloration of the teguments, adherence of the skin to the deep osseous or cartilaginous structures, and a mottled appearance of the skin with telangiectasis. In other cases there appeared a chronic myositis sometimes composed of simply a muscular retraction; at other times by a muscular inflammation simulating a diffuse glandular recurrence. The sensation of painful muscular contraction in the entire irradiated region has been noted five to six years after treatment without a single muscle appearing to be especially diseased.

All these symptoms can be the sign of graver chronic lesions, such as radiodermatitis with ulceration of the dermis and secondary infection, and osteo-radionecrosis or chondro-radionecrosis which can cause death by infection or hemorrhage. The late rupture of vascular walls in the neighborhood of a radionecrotic zone in the soft parts has been observed several times. Furthermore the vessels have often been

modified by the irradiation even in the absence of radionecrosis in their zones or neighborhood; particularly the formation of aneurysmal dilatation in the region of the carotids two years after treatment has been observed in 4 patients.

In certain cases of intense irradiation with cure, we have observed late neuritis with muscular atrophy and more or less complete paralysis of the subspinous muscle, deltoid, and trapezius; they appear to be the result of compression of the nerve trunks of the cervico-brachial plexus by the deep sclerotic connective tissue; sometimes it was only a simple local neuritis without muscular atrophy of appreciable weakness.

We have also observed following very extensive intense irradiation for epitheliomas of the tonsillar region, deafness due to sclerosis of the tympanic membrane and ossicles appearing three to six months after treatment, and cataract formation developing two years after irradiation when ocular protection has been impossible.

Most of these immediate or late local accidents are avoidable:

(a) By watching and reducing the intensity of the treatments, i.e., by lengthening as much as possible the total duration of the treatment when the neoplastic lesions are larger and the fields of exposure cover a greater surface area. If for fields of 80 sq. cm. the treatment is extended over 20 days, the same skin doses should be extended over 25 to 30 days for fields of 150 sq. cm. A dose of 6 H (about 600 r) daily should usually not be exceeded. A dose of 50 H which can be given in 10 days over a single field of 50 sq. cm., should be reduced to 35 or 40 H and given in 16 to 17 days for a single field of 150 sq. cm.

(b) By taking prophylactic measures against the secondary causes of accidents. In order to fight against the possibility of osteo-radionecrosis of the inferior maxilla which we have observed one, two and even five years after treatment of epitheliomas of the tonsillar region, we at one time made a practice of resecting the angle of the inferior maxilla before treatment. This meth-

od, however, did not yield favorable results.

The extraction of all teeth on the side of the lesion, meticulous cleaning of the teeth on the opposite side, with the extraction of roots and teeth in bad condition, are essential and constitute the minimum of precaution. We thus avoid infection, the essential cause of osteonecrosis, and we avoid the possibility of extraction after treatment at an inopportune time, which has nearly always been the cause of necrosis of the inferior maxilla.

In order to avoid osteo- or chondro-necrosis following roentgen therapy of epithelioma of the larynx or hypopharynx we have made a practice of resecting the thyroid and cricoid cartilage on the side of the lesion, especially when they were frankly ossified. This operation which is advantageous becomes indispensable when the cancer has invaded the cartilages, is deeply infected and only slightly radiosensitive. Most of the bony or cartilaginous necroses of the larynx are due, in fact, much more to the invasion of the cartilage by the neoplasm than to the effect of irradiation.

The accidents which we have just described are much less likely to occur when we take these precautions and when the treatments are divided over a longer time, using larger fields. But in these cases of very extensive fields, other varieties of accidents appear: these are the complications or accidents of a general nature; they can be early or late

3. *Early and late general complications.* Those that appear first are the disturbances of the digestive apparatus, such as nausea and vomiting. They are very frequent complications but they are often of little importance. They occur more frequently in women than in men. They indicate the limit of individual tolerance. It is only necessary to lower slightly the daily doses and to reduce the size of the fields to cause the symptoms to disappear without discontinuing the treatment.

The hepatic complications are more serious. They are characterized by a passing

subicterus with elevation of temperature, but we have sometimes found, besides a marked and persistent icterus, an enlargement of the liver accompanied by a sensation of local tension. In 2 cases where the treatment was intense with rather large fields, the jaundice ended in death, occurring twenty-five days after the beginning of the treatment in one of the patients and three months in the other.

The slight hepatic disturbances have often been accompanied by cutaneous manifestations of a toxic nature which appear sometimes five to six days, one month, and more rarely, two to three months after the beginning of treatment. The most frequent have been: erythema nodosum, especially located in the legs; urticaria, in the thoracic, abdominal and brachial regions, and palmar or plantar eczematoid eruptions. The duration of these cutaneous manifestations was at the most one to one and a half months. Diverse inflammations or articular congestions of the same nature have been observed at different times. These generally less serious complications have not influenced the progress of treatment.

It is different with the cardiac complications. They often constitute an obstacle to the completion of the outlined irradiations. They are characterized, after two or three weeks, by a marked asthenia, a lowering of the maximal arterial tension with a tendency to annul the pulse pressure. These symptoms are sometimes accompanied by signs of acute or chronic myocarditis and as we have observed in 2 cases, can cause death. They are always marked when we utilize large fields, even if the daily doses are weak; they are rare if we use small fields, even if the daily doses are high. They can be attributed to the association of toxic phenomena (liberation of chemical products especially from the connective tissue). In the cardiopaths, roentgen therapy of cancer is always very difficult and very imperfect. The results are usually unsatisfactory on account of the impossibility of regular treatment even if the size of the fields is reduced. In these patients bron-

chopneumonia is a frequent complication and sometimes occurs during the radioepithelitis, when the larynx and hypopharynx are filled with false membranes.

The loss of weight is often considerable during the course of treatment. When the doses and the fields are not proportioned to the tolerance of the patient, the loss of weight may reach 15 to 20 kilos in one month. Thus, in a patient who has been weakened and emaciated previously by the development of the epithelioma, this additional loss of weight as a result of roentgen therapy still further reduces the chances of success.

In the cervical regions, a field of 150 sq. cm., with daily doses of 400 to 500 r, causes a rapid loss of weight. If cervical fields, not exceeding 50 to 60 sq. cm. are utilized, the

loss of weight is generally negligible even for the high doses. In the tuberculous the loss of weight is very rapid and often compels a postponement of the treatment.

After the cancer has disappeared, the patient rapidly regains the lost weight. Some of these, however, regain only a small part of their weight; they are the patients in whom the treatment has been poorly adapted to their physiologic state and whose organism has been greatly modified. They remain extremely delicate and the slightest intercurrent affection takes on a grave aspect. Three of our patients in whom the treatment was too intense have died.

We have encountered no changes in the blood picture which could be considered as a complication.*

* For discussion see page 343.

