Clostridium botulinum. When series of duplicate sets of tubes are heated, it is noted that there is no sharp line of demarcation on one side of which it can be said that all the tubes show growth and on the other side of which all are sterile. There is considerable irregularity, with the occurrence of skips, which show that in some tubes which have been submitted to a longer exposure to heat, the spores have survived, whereas in others in which the exposure was considerably shorter, they were all destroyed. Similar results were observed by actual count of surviving bacteria in sets of agar tubes. In the tubes which show surviving spores there is a gradual decrease in the number up to a certain point, at which the drop is sudden and beyond which but few survive. Beyond this point there may be persisting growth after considerably longer exposures to heat, although only one or two colonies develop in each tube.

From observations based on approximately 40,000 tubes, it appears that about 95 per cent. of the spores are destroyed comparatively quickly, and that among the remaining 5 per cent. there are a few spores which are much more resistant. If this is true, it explains why only a few tubes in a series show the maximum heat resistance time, or a few cans in a pack show botulinus contamination, and also suggests as a reason for the average lower resistance time when but few spores are present in the heating mixture, that among the few spores there is less probability of a highly resistant spore being present.

3. There may be very marked delay of germination of spores of *Clostridium botulinum* after they have been heated. In practically all experiments it was noted that some of the tubes would remain apparently sterile for weeks or months after the others had shown growth, but would eventually show vigorous growth with toxin formation. The longest delay which has thus far been observed is 330 days.

The causes of this delayed germination of heated spores are not yet apparent. An analogous condition occurs in normal, unheated botulinus spores, but has

MAXIMUM SURVIVAL TIME IN MINUTES OF SPORES OF
CLOSTRIDIUM BOTULINUM WHEN HEATED AT
DIFFERENT TEMPERATURES IN DIFFERENT SUBSTRATA

Temperature Heated in Degrees C.	Broth	Brain	Oil Stratified Broth
100	225	270	315
107.5	40	45	80
115.5	7	10	42
121	4	6	22

not been demonstrated for so long a time. Whether the heating increases the normal tendency to dormancy or whether the dormant normal spores are the more resistant ones has not been determined.

4. The age of spores which have been kept at room temperature in the culture medium in which they developed does not materially influence their resistance to heat after their equilibrium of resistance has been reached. It was found that spores in a culture aged 22 days were considerably less resistant than those in a culture of 66 days, but that between 66 and 315 days the resistance was practically constant.

5. The reaction of the material in which the spores are heated plays an important part in determining their resistance to heat. The maximum resistance exists when the medium is approximately neutral, and rapidly decreases as the hydrogen-ion concentration approaches both the acid and alkaline ranges. There is a much

narrower zone of greater resistance at higher than at lower temperatures.

Parallel studies of hydrochloric, citric, acetic and lactic acids by sealed tube technic were complicated by the fact that the bacteria were incubated in the mediums in which they had been heated; but there seemed to be no appreciable difference in the resistance of the spores at corresponding hydrogen-ion concentrations of these acids.

6. The kind of medium in which the spores have grown does not seem to influence their heat resistance, but there is a variation in the heat resistance, depending on the type of substratum in which they are heated, which is not dependent on any difference in reaction.

When spores are heated in broth of approximately neutral reaction, they are more quickly destroyed than when they are heated in brain medium of like reaction; and if a thin layer of oil is placed on the surface of the broth, there is a greatly increased survival after the heating process.

7. The maximum survival times for *Clostridium botulinum* which have thus far been obtained in this series of experiments in sealed tubes are shown in the accompanying table. It will be noted that the survival time at 100 C. falls considerably short of that obtained in open tubes, which was six hours.

INTENSIVE DEEP ROENTGEN IRRADIATION

A STUDY OF THE IMMEDIATE EFFECTS

J. HENRY SCHROEDER, M.D.

CINCINNATI

My observations are based on a series of 100 intensive deep roentgen irradiation doses that I have applied since therapeutic apparatus for this purpose has become available in this country. The term "intensive deep irradiation dose" is used to describe a quantity of roentgen rays that is absorbed by deep tissues and sufficiently large to bring about certain biologic and clinical results.

I record primarily the observations concerning the immediate effect of this newer method of roentgen irradiation on the patient, and the physical reaction.

It is well established that the absorption of large irradiation doses leads to certain more or less transient effects on the patient. Recourse to this newer form of therapy is, therefore, determined not only by the probable local result but also, and properly, by the effect that exposure to the intensive irradiation will have on the individual.

Understanding of the effect of irradiation depends on one's conception of the process of intensive deep irradiation. To avoid the use of technical terms in which workers in this field have come to think, I shall briefly describe, as the basis for these observations, the factors that determine the character of the irradiation.

TYPE AND QUANTITY OF ROENTGEN RAYS

The roentgen rays applied in this series were produced at a voltage of from 200,000 to 220,000, using a Coolidge deep therapy tube. They were filtered through copper filters, from 0.5 to 1 mm. in thickness, according to the penetration and depth dose desired. An area of entrance of the rays was as large as possible, but not exceeding, as a rule, 20 by 20 cm. In

one case the area included an entire side of the chest. The distance from the anode to the skin varied in different cases between 50 and 80 cm., depending on the depth dose desired.

The unit of measurement in this series is the erythema dose, as determined by Wintz, or the quantity of ultrahard rays, absorbed by the skin, which produces an erythema in ten days in the average case. His "carcinoma dose" is from 100 to 110 per cent. of this surface dose of ultrahard rays administered deep into the body tissues. The required dose for certain other pathologic conditions has been determined as somewhat less. The measurements were made by the Wintz iontoquantimeter, and the transformer, the tube and the filter were carefully calibrated by this instrument, which is reliable. All results in deep roentgen therapy in German clinics have been made possible only through the advantages of the iontoquantimeter.

PROTECTION OF THE PATIENT

Irradiation effects are due primarily to the amount of roentgen rays absorbed by the tissues through the treated areas. The effects may be aggravated by

GENERAL EFFECTS

The general constitutional effects have been surprisingly mild. The patients have felt somewhat indisposed; loss of appetite sometimes persisted for a week. Occasionally there was some nausea, but rarely vomiting. None of my patients reacted so badly as to become confined to bed from irradiation effects, although they had received full irradiation doses of the type described, through rather large masses of tissue. In general, the unpleasant effects from hard rays have been very much less noticeable than from soft rays.

Blood examinations tend to confirm the conclusion of other investigators, that no matter what region is subjected to irradiation, there is a marked effect on the blood-forming organs. Within the first three days there is generally a marked reduction of lymphocytes, and often an improvement in the red cell count. At the end of a week, the blood picture begins to be restored, and at the end of six weeks it has approached the normal again in favorable cases.

The blood counts in the accompanying table illustrate the effect of heavy irradiation.

A rise of temperature amounting to not more than a fraction of a degree was observed now and then. It

EFFECT OF INTENSIVE DEEP ROENTGEN IRRADIATION ON BLOOD PICTURE *

Date	Per Cent. Hemoglobin	Red Blood Cells	White Blood Cells	Poly- morpho- nuclears	Eosino- phils	Baso- phils	Lymphocytes		Transi- tionals	Myelo- cytes	Large Mono- nuclears	Area Irradi- ated
							Large	Small				
Before irradiation												
1/19/22.....	80	5,135,000	6,225	56	7	..	3	33	..	..	1	
After irradiation												
1/23/22.....	80	5,120,000	5,225	66	2	..	2	26	4	..	..	Thigh
1/26/22.....	80	5,020,000	5,850	66	6	..	3	24	1	..	..	Thorax
1/30/22.....	80	4,750,000	3,950	69	3	..	3	21	4	..	..	Thorax
2/ 4/22.....	80	4,430,000	3,800	65	8	3	4	20	..	..	..	Thigh
2/10/22.....	80	4,740,000	3,750	4	10	..	14	3	..	..	1	
Patient discharged from hospital; period of recovery; no further irradiation until March 18, 1922.												
Before new irradiation												
3/18/22.....	..	4,050,000	5,350	59	..	..	4	28	9	..	..	
After new irradiation												
3/28/22.....	..	4,120,000	3,750	62	..	..	6	32	..	..	..	Thigh
4/ 3/22.....	70-80	4,180,000	3,950	68	..	..	4	27	1	..	..	Thorax
4/ 7/22.....	70-80	4,040,000	3,350	62	1	..	4	24	6	..	3	Thorax
Period of recovery; no further irradiation until June 27, 1922.												
Before new irradiation												
6/27/22.....	70-80	4,530,000	4,975	60	4	2	2	29	8	..	..	
After new irradiation												
6/30/22.....	70-80	3,700,000	5,550	74	1	..	2	23	..	..	..	Liver
7/ 1/22.....	70-80	3,630,000	5,600	65	..	..	1	34	..	..	..	Thigh
7/ 6/22.....	70-80	4,450,000	3,550	63	4	2	4	23	4	..	..	

* The patient was being treated for sarcoma of the thigh with metastases in both lungs and in the liver. Dates under "after new irradiation" designate time of separate doses.

unwonted absorption through insufficiently protected areas that are not being treated, and through continuous breathing of the contaminated air that is often present in the treatment room. In my cases, the diffusion of the rays was limited as much as possible by the usual lead glass tube holder and lead-rubber treatment cones. The patient is covered entirely with heavy lead-rubber, except over the treated area. The possible absorption of extraneous rays is thereby reduced to a minimum. The absence of wires eliminates corona discharges, and thorough ventilation eliminates even traces of nitrous gases. The patient rests on an insulated table.

All treatments had for their aim the administration of the required dose in one sitting, or as few sittings as the patient's condition permitted. The longest exposures have been in the most superficial cases. The longest continuous exposure lasted six hours; other cases have required two periods of four hours each in one day; one patient with traumatic sarcoma of the thigh, with metastases in both lungs, received three sarcoma doses within ten days.

was sharply defined after irradiation of the liver for metastatic sarcoma, as shown in the accompanying chart.

LOCAL EFFECTS

The local effect is manifested on the skin, on the superficial organs such as glands, and on the organs subjected to irradiation.

The Skin.—An erythema was produced in all cases in which the full dose was administered through one area. It varied in degree with different persons. When the pathologic tissue was situated close to the surface, I was required to administer very full erythema doses. In one case of multiple, superficial, large carcinomatous masses, there appeared immediately after treatment three areas of erythema that remained three weeks, with the rather annoying accompaniments of a dermatitis of that degree. The skin recovered fully without denudation, and in six weeks the carcinomatous masses had disappeared, with the exception of a still palpable axillary gland. In the course of these treatments I have not seen blisters produced, necrotic areas, or telangiectases of the skin.

The erythema is followed by a transient, faint brown-ing of the skin.

When more than one area may be utilized for entrance of the rays, it is rarely necessary to produce an erythema, because the skin dose may be so appor-tioned on the basis of iontoquantimeter calculations that an erythema is avoided.

The Glands.—There is usually an enlargement of the superficial lymphatic glands in the irradiated region, which subsides after two or three days. When the region of the neck is irradiated, the effect on the salivary glands leads to an annoying dryness of the mouth, and there is usually an enlargement of the parotid glands. In one case of sarcoma of the naso-pharynx, I administered the full sarcoma dose in one sitting of four hours. Because of the massive glandu-lar involvement on each side of the neck, it was to be expected that the salivary glands could not be spared. The sarcomatous masses disappeared entirely within twenty-two days, but the trying dryness of the mouth remained for months.

The Nerves.—It is worthy of record that in two cases in which the chest was irradiated, a true herpes zoster occurred soon after the irradiation. One was a case of metastatic carcinoma of the lungs, and the other was an inoperable case of cancer of the breast. The herpes occurred in the latter case on the side of the lesion. The rays had been applied only from the an-terior aspect. I can-not prove any caus-ative relationships between the disease, the treatment and the herpes.

The Lungs.—Full irradiation doses, ap-plied to the lungs for cancer or sarcoma, gave rise to a feeling of "tightness in the chest." There was bron-chial irritation in each instance, and in the case of metastatic carcinoma of the lungs, from mammary can-cer, there was slightly blood-streaked sputum for sev-eral days. It is my opinion that these manifestations correspond to a surface erythema reaction.

The Esophagus.—I have observed a marked imme-diate effect in only one case of temporary complete cancerous occlusion of the lower portion of the esophagus. The patient was unable to swallow either hot or cold water on the day of the treatment. Twelve hours after the intensive irradiation, the patient tele-phoned me that he was able to swallow a cupful of water "and two bottles of pop." This man was able to take soft food without regurgitation during three weeks after that, when occlusion again occurred. A second treatment permitted him to take food for another three weeks, again followed by occlusion. At that time a gastrostomy was performed for relief. The patient died in about one month after operation.

The Bladder.—Immediate effects have been observed in malignant disease of the bladder, as evidenced by production of subjective symptoms, or modification of symptoms, and by cystoscopic examination, and in cases in which the bladder was not directly involved but bladder symptoms were produced by involvement

of the vesicovaginal wall. In intravesicular disease, I have found the bladder exceedingly sensitive to roentgen irradiation. The bladder irritability was much increased. If there was pain prior to the irradi-ation, it became more severe after the treatment. All the subjective symptoms subsided in the measure that the local condition improved. When there was bladder irritability from involvement of adjoining organs, I have observed entire disappearance of this complaint from the moment that deep irradiation was applied.

When there was discharge of blood and pus from the bladder in the course of the disease, this discharge became gradually less in the course of a week after the irradiation. A noteworthy observation was the pres-ence in the urine of shreds of necrotic tissue after the administration of carcinoma irradiation doses to the bladder.

Cystoscopic Observation.—In a number of cases I had the advantage of cystoscopic observation of the bladder wall of patients suffering from carcinoma of the bladder. The patients were observed immediately prior to, and one week after the irradiation. The immediate effect on the malignant ulceration, as seen one week after the irradiation, was, to use the sur-geon's own words, "miraculous; the ulcerated area

decreased one-half in size." In other cases the information was that the mass was sloughing. In all these cases there was observed a strong re-action in the bladder wall. Since a full erythema depth dose was given, controlled by iontoquantimeter measurement, the local reaction, which was expected, un-doubtedly corre-

Small but well-defined rise in temperature after irradiation, July 1; temperature previously normal (sarcoma).

sponds to a surface erythema. The reaction, in connec-tion with the demonstrated necrotic process in the malignant mass in the bladder, tends to support the theory advanced by some pathologists that the disap-pearance of malignant tumors in some areas and in some tissue elements, after irradiation, is possibly due to the effect of the irradiation on the blood vessels sup-plying the neoplasm, causing their obliteration and, con-sequently, necrosis in the mass. It is possible that this process has its effect on the type of carcinoma occurring in the bladder.

The Abdomen.—After full erythema doses to the deep abdominal tissues, I have regularly observed increased intestinal irritability, evidenced by more fre-quent evacuations. The systemic effects are more noticeable, and the nausea occurs rather promptly. In a case of tuberculosis of the peritoneum, in which for some time before their irradiation a gallon of fluid had been aspirated every two weeks, there was no further exudate after the second dose, and the tuberculous masses, formerly very distinct and palpable, had entirely disappeared.

SUMMARY

1. Large doses of intensive, deep roentgen irradi-ation with ultrahard rays, with proper precautions, have been safely administered to patients who were not cachectic.

2. The general systemic effect is, under these conditions, less distressing than formerly, after irradiation with the soft rays.

3. The immediate effect on the blood and blood-forming organs is marked, but restoration begins as a rule within a week after the irradiation in noncachectic cases. Hemorrhages from internal malignant growths ceased; this result alone is of immediate benefit to the patient.

4. The immediate effect of therapeutic doses on the deeper organs in irradiated areas is that of irritation, and probably corresponds to a surface erythema. Glandular tissues may be destroyed.

5. In noncachectic patients, a surface erythema from these ultrahard rays was safely produced when necessary. It must be attained whenever a malignant mass near the surface is to be treated through one area of entry.

6. The iontoquantimeter permits the administration of the desired and known depth dose, and is the basis of scientific deep roentgenotherapy.

11½ East Eighth Street.

THE SIMULTANEOUS OCCURRENCE OF TUMORS IN THE THYROID, UTERUS AND BREAST

MAX BALLIN, M.D.
AND
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DETROIT

Every surgeon who operates upon goiters must have noticed the frequent occurrence of tumors in the thyroid, uterus and breast. Apparently there has been very little written on the subject, however, for we could find only two references in the literature. Falta's¹ "Ductless Glandular Diseases" contains this note:

There seems to exist a certain relationship between goiter and myomata of the uterus. At least it has been observed that in strumous women who also suffer from myomata the struma also decreases in size with the retrogression of the myoma at the menopause.

Falta's note is quoted from an article by Ullman² of Vienna. This article reads:

It has been known for a long time that a relationship exists between the uterus and the normal thyroid gland. The nature of this relationship is, of course, enshrouded in darkness; we only know that in a not infrequent number of women a transitory enlargement of the thyroid gland takes place at the time of menstruation. After the cessation of menstruation, the thyroid returns to normal. . . . In many women during pregnancy an enlargement of the thyroid takes place, which still exists after childbirth. . . . A third fact which concerns the question of the relationship between uterus and thyroid is that as to whether strumas develop more frequently in females than in males. . . . I wish to emphasize that in women affected with myomas I was able to show a distinct enlargement of the thyroid gland, an enlargement that could be spoken of partly as struma parenchymatosa, partly as the result of degeneration, as colloid struma. . . . I was then able to determine that these strumas following complete myomectomy became decidedly smaller; in many cases they disappeared entirely.

In looking over our own records, we find that of the last 100 female patients who consulted us for goiter, eighteen had fibroids;³ four of them also had breast tumors; and of the last 100 patients who consulted us for fibroids, thirty-five had goiter; six had breast tumors. Thus, of the total 200 patients, fifty-three, or 26.5 per cent., had tumors of both thyroid and uterus. Ten of these 200 patients required operations on both the thyroid and the uterus. This large number of multiple lesions is obviously much more than a coincidence; yet, as noted above, very little mention of it has been made.

The matter therefore seemed important enough to call attention to again. Three points suggest themselves:

(a) It is possible, as suggested by Ullman, that certain goiters might be reduced in size or even cured by removal of a fibroid.

(b) Thyroid extract and iodine might be beneficial in preventing the development of fibroids as well as of goiters.

(c) These relationships might have some bearing on the etiology of these tumor groups.

In the eighteen goiters found in the examination of 100 fibroids, fourteen were adenomas of the thyroid, three were colloid goiters, and one was an exophthalmic goiter. Of the four breast tumors which accompanied goiters, an adenofibroma with cyst-areas accompanied an adenomatous goiter; an adenoma of the left breast accompanied an adenomatous goiter; an intracanalicular adenofibroma in the right breast, and a similar tumor with hyaline changes in the left breast accompanied a colloid adenomatous goiter. Another goiter which is not tabulated showed virginal hypertrophy of the right breast. Of the six breast tumors which accompanied fibroids, three were interstitial mastitis; one was a fibro-adenoma; one was a carcinoma of the left breast and fibro-adenoma of the right breast, and one was a cystadenoma.

Of the fifty-three patients with the combination of goiter and fibroid, the youngest was 25 years old, this patient being the only one below 30. Fully two thirds were over 35. We may say, therefore, that the incidence mounts with age, the simultaneous occurrence of goiter and fibroid being most prevalent in the latter half of the third decade and during the fourth decade. Of the 100 goiter patients, twenty-one were under the age of 25. There were no fibroids among these patients, so that the percentage of eighteen fibroids is borne by seventy-nine patients more than 25 years of age. In other words, the fibroid-goiter combination shows its entire incidence after 25 years of age, and increases rapidly after 35 years.

The simultaneous occurrence of goiters, fibroids and breast tumors is more frequent than is usually supposed. The thyroid, breast and uterus have different anatomic structures and are different in their embryologic origins, but we note that the function of the thyroid is closely related to, and influences the function of the sexual organs. The interrelationship of uterus and breast is obvious. Since these organs are related to each other only by function, it must be that physiologic interdependence is a factor in the tumor formation.

When sexual function ceases or begins to wane, usually the time arises for the growth of all these

1. Falta, Wilhelm: *Ductless Glandular Diseases*, Philadelphia, P. Blakiston's Son & Co., 1916, p. 156.

2. Ullman, Emmerich: *Ueber Uterusmyom und Kropf*, Wien. klin. Wchnschr. 23: 585, 1910.

3. Though some patients had large uteri, no diagnosis of fibroid was made unless there was a certainty of this condition.