RODENT ULCERS: AN ANALYSIS OF 711 LESIONS TREATED BY RADIOTHERAPY

BY

IAN CHURCHILL-DAVIDSON, M.B., B.Chir.
D.M.R.T.

Assistant Radiotherapist

AND

ETHEL JOHNSON, M.B., B.S., D.M.R.T.
Late Senior Registrar

Department of Radiotherapy, St. Thomas's Hospital, London

Many papers have been published on the subject of rodent ulcers and their treatment by radiotherapy; in all those we have examined there is almost complete agreement on the excellent results produced, from the point of view of both cure and cosmetic appearance, in early lesions not previously treated. Some papers give no cure rate at all; others mention it in what can only be described as an expression of opinion, since it is unsupported by figures and at first sight these "cure rates" may appear unduly optimistic to a non-radiotherapeutic eye. Finzi (1933), for example, stated: "In the early stages, the method of radium treatment advised will cure 99% of cases." Windeyer (1951) said: "The great majority of all rodent ulcers occurring on the skin of the face or neck are treated by radiotherapy, and if they are still free from involvement of underlying bone or cartilage they are curable . . . to the order of 95% by this means."

That there is justification for these high percentages is seen by a study of other works, which give figures showing clearly how the cure rate is arrived at. In 1935 Magnusson gave $93.3\% \pm 2$ as his highest estimated three-year cure rate for superficial lesions, using mainly radium. In 1946 Mustakallio's net three-year cure rate for superficial lesions less than 1 cm.² was 97.8%, using both x rays and radium. Stanford Cade's (1952) three-year cure rate for a series of Stage I (involving skin and subcutaneous tissue only) rodent ulcers treated from 1925 to 1937 was 98%, using radium only. The highest disease-free rate for Stage I basal-cell carcinomata mentioned by the National Radium Commission (1937-8) is 99%. It must be emphasized, however, that these cure rates refer to early lesions only and to treatment mainly by radium.

The use of different methods of expressing results is one of the factors that make precise comparison of the above percentages very difficult. How much more difficult, then, is it to compare results of whole series, each of which is made up of lesions at all stages of development. Although no attempt at comparison is made here, the results of three centres are shown in Table I, and readers are referred to the original works for further information.

In stating the excellence of the results of radiotherapeutic treatment of basal-cell carcinomata most papers lay emphasis on the part played by radium. It was therefore felt that the time had come to demonstrate the results of x-ray therapy and to show that equally satisfactory results could be obtained with suitable x-ray techniques, which on the whole are easier to apply than radium and subject the patients to less inconveni-

TABLE I.—Results of Three Centres in the Treatment of Rodent Ulcers by Radiotherapy

Author and Centre	No. of Tumours	Method Used	Net 3-year Cure %	Absolute 3-year Cure %	Estimated 3-year Cure %
Magnusson (1935). Radiumhemmet, Stockholm	521	Radium only			86.8 ± 1.5*
Mustakallio (1946). Central Inst. Radiotherapy, Helsinki	660	X rays and radium	95.7	67.7	
Smithers (1952). Royal Cancer Hosp., London	500	X rays only	90.6†		

* Magnusson's figures include cases of recurrence after previous treatment.

† Life-table method. 90.6% applies also to the fourth and fifth years.

ence. This paper has been written with that object in view.

Survey of the Material

We have reviewed all cases of rodent ulcer treated primarily by radiotherapy at St. Thomas's Hospital during the years 1939 to 1950 inclusive. The total number of patients so treated was 653; of these we have excluded 40—that is, 24 in which the case details were inadequate, 12 in which the diagnosis was doubtful, and 4 which did not complete treatment. This left 613 patients, of whom 63 (10.3%) had more than one lesion treated, as shown in Table II, making a total of 711 treated lesions.

TABLE II.—Number of Patients with Multiple Treated Lesions

No. of lesions treated	2	3	4	5	6	11
No. of patients	44	13	3	1	1	1

Sex and Age Incidence (Table III).—The disease was shown to be slightly more common in men, with a slight tendency for men to develop the lesions earlier than women. In both sexes the disease was most frequent in the seventh decade.

TABLE III.—Sex and Age Incidence

Age:	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91-100	
Men	4	27	65	71	81	64	13	0	325
Women	3	20	39	44	95	68	17	2	288
Total	7	47	104	115	176	132	30	2	613

Aetiology, Site, and Type Incidence.—There seemed to be no significant increase in the incidence in patients whose occupation was largely or wholly outdoor. Lesions are said to be most common on the face and neck, especially above a line joining the tip of the lobule of the ear with the angle of the mouth; they may, however, occur on any part of the skin surface (Table IV). Our series confirmed this, but

TABLE IV.—Number and Percentage of Rodent Ulcers at Each Site in Both Sexes

Site	No.	%	Site	No.	%
Scalp	9	1.3	Lower lip	4	0.6
Forehead and temple	148	20.8	Cheeks	171	24.0
Upper eyelid	3	0.4	Naso-labial fold	5	0.7
Lower eyelid	27	3.8	Chin	8	1.1
Inner canthus	59	8.3	Neck	29	4.1
Outer canthus	12	1.7	Trunk	15	2.1
Nose	164	23.0	Extremities	5	0.7
Ear	27	3.8			
Upper lip	25	3.5	Total	711	99.9

there was a bigger incidence of lesions in sites other than the face and neck in women than in men—only 2 lesions (0.5%) in men as compared with 18 lesions (5.2%) in women. Apart from this there was little or no difference in the site incidence between the sexes. Rodent ulcers may appear in several clinical forms, which have been variously named and classified by different authors. One form may change

into another as growth proceeds. The classification which we have adopted and the percentage incidence are as follows: (1) ulcerative, 69.2%; (2) papular, 7.7%; (3) cystic, 5.3%; (4) plaque, 10.5%; (5) superficial, 5.3%; (6) pigmented, 1.4%. There was no significant sex difference in the type incidence.

Size of Lesions at Beginning of Treatment.—These are shown in Table V. Some rodent ulcers penetrated fairly deeply, but none had apparently invaded cartilage or bone; those that did, being unsuitable for radiotherapy, were treated surgically. An attempt was made to correlate the extent of the lesions with their duration. No direct relationship, however, could be found, and in fact many of the patients with the smallest lesions gave the longest histories. Contrary to what one might expect, women did not seem to seek treatment earlier than men.

TABLE V.—Size of Lesions at Beginning of Treatment

Size of Lesions in cm. ¹	<1	1–	2–	3–	4–	5–	10–20	>20	
No.	364	185	43	41	24	39	10	5	711
%	51.1	26.0	6.0	5.8	3.4	5.5	1.4	0.7	99.9

Biopsies.—Clinical diagnosis of rodent ulcers is usually accurate in radiotherapeutic centres where large numbers of skin cancers are seen. A biopsy was therefore thought to be unnecessary in all cases. In this series 228 lesions (32%) were confirmed by biopsies, including a few cases in which the clinical diagnosis was in doubt.

Methods of Treatment

X-ray therapy was used in 703 (98.9%) lesions. The type of apparatus used—that is, low-, medium-, or high-voltage units with the range of 45–220 kV—varied with the estimated penetration of the lesion. The majority (595 lesions) were treated with a 60-kV unit. Radium or radon in the form of an applicator or implant was used in only 8 cases, which were technically difficult to treat with x rays.

All X-ray treatments were classified into the following three groups:

(I) *Single Dose.*—This method was used only in small and very superficial lesions, the prescribed dose being given in a single application; 171 lesions were so treated, 159 at doses between 2,000 and 3,000 r.

(II) *Fractionated into one or two treatments a week over a period of one to three weeks.* The lesions included in this group were all superficial and small to medium in size; the total number treated was 150, of which the majority received a total dose of between 3,500 and 5,000 r.

(III) *Fractionated into three to five treatments a week over a period of one to three weeks.* Most of the earlier cases in the series were treated by this method irrespective of their size or penetration; but since 1948 it has been our policy to reduce the number of treatments so as to minimize the inconvenience to the patient. This form of treatment has therefore been reserved for the larger and/or more penetrating lesions. In the vast majority the treatment was given over two weeks, and the total dose varied between 4,500 and 6,500 r.

The dosage and fractionation used from 1948 onwards are summarized in Table VI.

TABLE VI.—Dosage and Fractionation in Use Since 1948

Diameter of Treatment Area	Degree of Penetration of Lesion		
	Superficial	Moderate	Deep
	Low-voltage Therapy	Medium-voltage Therapy	High-voltage Therapy
<2.5 cm.	3,600 r, 3T, 14D or 2,300–2,500 r, single dose	3,300 r, 3T, 14D	4,000 r, 15T, 21D
2.5–5 cm.	3,600 r, 3T, 14D	4,000 r, 10T, 14D	4,000 r, 20T, 28D
5–10 cm.		4,000 r, 15T, 21D	
>10 cm.			

T=Treatments. D=Overall time in days.

Results of Treatment

In expressing these results it was decided to use a net cure percentage (as being the most accurate method in this disease, in which there is such a high rate of cure). This is usually estimated by subtracting those who have died and disappeared free of cancer symptoms from the total number of lesions treated, and calculating the symptom-free rate from the remainder. Table VII shows, however, that we have also deducted from the total 14 cases (3 in women, 11 in men) which underwent little or no regression following maximum dosage. We are aware that these cases would be classified as recurrences in some centres; but, since we define recurrence as the reappearance of evidence of disease after a period of complete apparent tumour regression, in our opinion they should be classified separately as primary radiation failures in that they are for all practical purposes completely resistant to radiation. In this series they formed 1.9% of the total number of lesions.

TABLE VII.—Results of Radiotherapy in 711 New Basal-cell Carcinomata in Both Sexes, 1939–50

No. of Years Since Treatment	No. of Lesions Treated	Cases of No Regression	Died of Inter-current Disease cancer-free	Un-traced	Recurrences	Symptom free	
						No.	%
2½–3	95	2	9	5	5	74	93.6
>3	616	12	62	51	21	470	95.7
>5	309	9	38	31	17	214	92.6

Table VII shows the results of radiotherapy in 711 previously untreated basal-cell carcinomata—366 in men and 345 in women. There was little difference in the symptom-free rate in men and women treated more than three and five years ago. The combined three-year symptom-free rate is 95.7% and that for five years is 92.6%. The symptom-free cases include seven of incomplete regression which required a second course of treatment before healing occurred.

Recurrences

Out of the total of 711 rodent ulcers there were 26 known recurrences, of which 8 were cured with further radiotherapy—4 of them for periods of over five years—and all 8 were symptom-free when last seen. Recurrence of basal-cell carcinoma following radiotherapy therefore does not always indicate incurability by radiotherapy, and second courses of treatment may cure; but it must be emphasized that this is possible only in recurrences which are small, and provided that the original dose was moderate and marked skin changes have not resulted, otherwise there is a serious risk of producing radionecrosis. The aim in radical irradiation, however, is and has been for many years to cure with one course of treatment and one only.

In an attempt to discover if recurrences had a predilection for any site, their distribution was compared with that of the primary lesions. The actual figures of recurrences at the various sites, however, were too small to be of any statistical significance.

Time of Appearance of Recurrences.—Most analyses show that the majority of recurrences appear within the first five years after irradiation and in diminishing numbers from the first to the fifth years. In those cases treated more than five years ago 17 recurrences were discovered, and, of these, 6 were found in the first year after treatment, 2 in the second year, 5 in the third, 1 in the fourth and the fifth years, and 2 in the sixth. Thus 76.4% of these recurrences were in the first three years and 88% in the first five years.

Recurrences Related to Size of Lesions.—Since difficulty is often experienced in assessing the depth of medium-sized lesions, it was decided not to attempt to make a division into superficial and infiltrating groups, but to show only

TABLE VIII.—Results Related to Sizes of Lesions

Size of Lesion in cm. ²	No. Treated	No response	Died of Inter-current Disease Cancer-free	Un-traced	Recurrences	Symptom-free	
						No.	%
<1	364	2	30	26	14	292	95.4
1-2	185	3	9	13	5	155	96.8
2-3	43	5	7	6	1	24	96.0
3-4	41	0	9	2	1	29	96.6
4-5	24	1	4	4	1	14	93.3
5-10	39	3	5	3	2	26	92.8
10-20	10	0	4	2	1	3	75.0
>20	5	0	3	0	1	1	50.0

the relationship between the number of recurrences and the surface extent of the primary lesions. Table VIII shows the results. It is interesting to note that 14 (53.8%) of the recurrences occurred in the first and the smallest group, indicating clearly that smallness of size is not the sole criterion of success in treatment. The recurrence-free rate is highest (96.8%) in the second group (1-2 cm.²), and thereafter remains remarkably uniform until over 10 cm.², when it drops; but the figures for the last two groups are too small for comparison.

Causes of Recurrence.—We have analysed the treatment details of all the lesions which have recurred to see whether any technical reason for the failure could be found. Nine cases were without doubt due to failure to irradiate a wide enough margin of apparently healthy tissue round the lesion, and one case was due to inadequate dosage. For the remaining 16 recurrences there was no obvious technical reason, but included among them were two advanced lesions.

Radionecrosis

There were seven cases of radionecrosis—one acute and six late. The acute case followed a moderate dose to a scalp lesion, and can only be ascribed to idiosyncrasy to radiation. It was successfully excised. The six late cases appeared five months to three and a half years after treatment. Four followed minimal trauma to the irradiated area, one followed sunburn, and one followed infection of the adjacent eye. In only two of the cases could the dose given be regarded as slightly excessive. No case followed the retreatment of a recurrence. Three cases had to be excised; the other three, however, amounted only to slight but persistent scabbing, and expectant treatment was adopted with success.

Cosmetic Results

The results obtained in 664 lesions treated by all methods are listed in Table IX. Cases of recurrence, necrosis, or no response are excluded. They may present a rather too optimistic picture, as there is a tendency for the cosmetic result to worsen slightly as time goes by. There was no evidence that the quality of radiation, dose (provided it is within the therapeutic range and not excessive), fractionation, or type of lesion has any direct relation to the cosmetic result which may be expected. Factors, however, which did appear to influence it were: (a) the penetration of the lesion—a deeply penetrating lesion never gave better than a fair cosmetic result; and (b) size of lesion—no excellent cosmetic results were obtained in lesions over 5 cm.² in area.

TABLE IX.—Cosmetic Results

Result	Both Sexes	
	No.	%
Excellent (no scar visible with normal inspection)	105	15.8
Good (pale scar with no pitting, pigmentation, telangiectasia, or contraction deformity)	508	76.5
Fair (slight pitting, pigmentation, telangiectasia, or contraction deformity)	39	5.8
Poor (marked changes as above)	12	1.8
Total	664	99.9

Comparison of Different Methods of Treatment

Any comparison of different treatment methods must take into account the extent of the tumours, and is thereby made the more difficult.

TABLE X.—Comparison of Results of Different Methods of Treatment

Method of Treatment	No. treated	No response	Died of Inter-current Disease Cancer-free	Un-traced	Recurrences	Symptom free	
						No.	%
X rays:							
Group I, single dose	171	3	16	10	5	137	96.4
Group II, 1-2 doses a week	150	1	15	9	2	123	98.4
Group III, 3-5 doses a week	382	10	38	37	18	279	93.9
Radium	8	0	2	0	1	5	83.3

It will be seen in Table X that the lowest x-ray results (93.9%) are in Group III, as one would expect, since it contains all the more advanced lesions. The highest x-ray results (98.4%) are in Group II, these being 2% better than those in Group I. The difference of 2% is statistically not significant, but the advantage of the Group II method is possibly more apparent when one considers that in many cases it was used for larger tumours than Group I. Nevertheless, it will be seen that the single-dose technique has proved a very satisfactory method for treating early lesions, thus confirming the results of Mallender (1950). It will also be seen that to date there has been no deterioration of results due to our policy of reducing the fractionation of the treatments in all but the large and/or penetrating lesions.

Finally, the results of the eight lesions treated by radium are shown, but it must be emphasized that the number is too small for fair comparison.

Summary

An analysis is made of 711 lesions treated by radiotherapy during the years 1939-50 inclusive. The sex, age, and site incidence are discussed and the sizes of tumours at the beginning of treatment are given.

Of the lesions 98.9% were treated by three x-ray techniques, the remaining eight by radium. Our policy in reducing the number of treatments over which the x-ray dosage is given, and the effect of this as regards both cure and cosmetic results, are discussed.

The cure rate for all lesions treated over three years ago is 95.7% and for all those treated over five years ago 92.6%. The results have been related both to sizes of tumours and to different treatment techniques. The cosmetic results obtained are given.

The incidence, cause, treatment, etc., of recurrence and radionecrosis are given and discussed.

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INTRAVENOUS ACETYLCHOLINE IN TREATMENT OF THE NEUROSES

BY

R. M. PHILLIPS, M.B., B.S., D.P.M.

AND

J. T. HUTCHINSON, M.D., D.P.M.

(From the Department of Psychological Medicine,
St. Thomas's Hospital)

A great deal is known about the actions of acetylcholine, but little has been written about its value as a therapeutic agent. It is known that cholinesterase rapidly destroys acetylcholine *in vivo*. Hence in using the drug intravenously the chief difficulty lay in choosing the optimum dose which would avoid the lesser danger of too rapid destruction and the greater danger of arresting the heart's action (Carmichael and Fraser, 1933). In spite of the handicaps a number of uses have been found for the drug, given as an intravenous injection. It has been considered an effective method of treating paroxysmal tachycardia (Martindale, 1952), and Williams (1941) found it helpful in the diagnosis of epilepsy, since it could provoke epileptic discharges in the E.E.G. records of certain epileptic patients. It was used first in the treatment of psychiatric patients by Fiamberti (1940, 1950), who gave intravenous doses of 600 mg., by which he produced syncope, unconsciousness, and often a convulsion. This approach was considered to be of value in treating the early stages of schizophrenia, and a recovery rate of 80% was reported. The basis for this form of treatment was the apparent similarity to the convulsive shock produced by leptaazol or E.C.T. Poort and Stigaard (1944) found that doses of up to 1,000 mg. could be injected safely. However, it did not gain wide repute, and unsatisfactory results were obtained by several workers, notably Harris and Pacella (1943).

A more modified form of treatment, using an intravenous dose of up to 200 mg. of acetylcholine chloride, was introduced in Spain by Lopez Ibor (1950, 1952), who found this approach useful in the treatment of certain neuroses and particularly of patients suffering from recurrent attacks of tension. Following a visit to Spain, Sargent (1952) introduced the treatment at St. Thomas's Hospital and reported on the initial findings.

The present paper describes a series of 211 patients who have been treated over a period of two and a half years at the same hospital.

Method

The Roche preparation of crystalline acetylcholine chloride was found to be the most reliable form of the drug. It was freshly prepared as a 10% solution in dis-

tilled water, usually as 200 mg. in 2 ml. The patients were given the injection intravenously, at least one hour after a meal, and initially a dose of 50 mg. was injected very slowly to test the sensitivity of the patient. This initial dose was then generally increased during subsequent treatments by 50 mg. to the total amount of 200 mg. A reaction usually occurred after the rapid injection of 50 mg. of acetylcholine chloride, but the remainder of the 200 mg. could then be given more slowly to prolong the reaction. Extra care has to be taken in those very sensitive to doses as small as 25 mg. The response took two forms: one showed coughing, flushing, salivation, lacrimation, sweating, etc., and was accompanied by momentary slowing of the heart; the other was primarily syncopal in form and was associated with prolonged cardiac arrest, unconsciousness, and convulsive movements. Physiological observations on these effects, including a description of a syncopal attack of 28 seconds, have been reported elsewhere (Phillips *et al.*, 1952). Barlow and Howarth (1953) have shown that the second, more severe reaction is similar to a Stokes-Adams attack. However, the aim of the treatment was to produce the first, milder reaction, and this could be achieved by gauging the rate of injection to suit the individual patient. There was little in the way of after-effects, and most patients were able to leave hospital five minutes after the injection, although the more elderly benefited from resting for 20 to 30 minutes afterwards.

Before a course of injections was begun the cardiovascular system was examined particularly, and in middle-aged patients a routine E.C.G. was done. It was also found possible to control attacks of spontaneous auricular fibrillation, which occurred in four patients, by giving a prophylactic dose of quinidine sulphate, 5 gr. (0.32 g.), half an hour before injections, and treatment could be continued. No fatalities occurred in over 6,000 injections when care was taken to gauge the dose correctly by gradually increasing speed and amount, especially in the sensitive patient.

The usual course of treatment consisted of 30 injections given over a period of six to ten weeks, depending on how often the patient was able to attend for treatment. Daily clinics have been held at St. Thomas's, and most patients found it possible to continue at work at the same time.

Results

The 211 patients consisted of 125 men and 86 women. The majority of patients who had this treatment, and incidentally the group which was helped most, suffered from symptoms which we have chosen to call "obsessive" (Sargent, 1952) or obsessional. These may result from exposure to stress, either psychological or physical, such as an acute debilitating illness, may start abruptly, and can often become self-perpetuating. The obsessional aspect of the condition commonly takes the form of a recurrent thought of an unpleasant nature or a particular phobia which is associated with a great deal of tension. This tension is experienced inwardly, and there is little or no overt evidence of its existence except the complaints of the patient. The reason why care has been taken to define this condition is because the drug proved to be of little value in the treatment of the classical obsessional neurosis, often dating from early childhood or accompanied by compulsive ritualistic behaviour.

Until it became clear that this particular obsessional group reacted best to this treatment, a wide selection of patients with anxiety symptoms were treated, including some in all of the following diagnostic categories: obsessional states as defined above, conversion hysteria, varied types of depression, schizophrenia, anxiety hysteria, classical obsessional neuroses, psychopathy, and chronic eczema.

Obsessional or Obsessive Tension States.—This category comprised 104 patients (Table I), of whom the surprisingly large number of 73 (70.2%) were improved by the treatment (Table II). Many were people who experienced the inner sense of tension already described, and they often