with none of the U.S.-U.K. series. The bed-rest cases had had no prophylaxis until after this assessment, and the U.S.-U.K. group were given penicillin followed by sulphonamide 1 g. daily in hospital and after discharge. Recurrences were more frequent in the unprotected group: some had more than one, whereas this never occurred in the protected group, and, as has been stated, many unprotected cases were worse after the recurrences whereas there was no deterioration in the protected. The type of case that did worse in the unprotected group, those admitted in second attacks with marked carditis, did not have recurrences while on prophylaxis.

We believe, therefore, that the differences in cardiac status at follow-up between the two groups of cases—one treated with salicylate or hormone in hospital and given prophylaxis and the other by bed rest and no prophylaxis—can be explained wholly by the beneficial effect of prophylaxis in reducing the number of recurrences and thereby the ultimate amount of cardiac damage, and that other drug treatment played no significant part. Thus our finding in the acute phase of the disease—that hormone therapy in the dosage we have used, though of value in special circumstances, does not significantly affect cardiac status in the majority of cases—has been borne out by the subsequent course at follow-up. The results emphasize, however, the value of prophylaxis, and show that this is the most certain method we have at present of reducing morbidity from rheumatic heart disease.

### Summary

The follow-up findings over a period of 5 to 10 years in 125 patients with rheumatic fever treated in this unit by bed rest alone and not given prophylaxis are considered separately in 19 who had recurrences and in 106 who did not. Patients without recurrences who had no abnormal heart sign in hospital were normal at follow-up; those with soft (grade 1-2) murmurs were normal or still had soft murmurs (none was worse); with more severe carditis (grade 3 murmurs) there was usually no change at follow-up, but in a few the signs were less (and some returned to normal) and in others more marked (increased aortic incompetence or development of opening snaps in addition to mitral systolic murmurs). With recurrences, however, there was often deterioration and sometimes death, especially in those admitted in second attacks or who had more than one recurrence.

Cardiac status on admission to hospital in these cases and subsequently at follow-up has been related to the total number of attacks of rheumatic fever or chorea. On admission in first attacks, most had no or slight carditis; in second or later ones the majority had marked heart disease. At the last follow-up the majority of those whose cardiac status had deteriorated (including deaths) had had three or more attacks, and mitral stenosis was observed to develop only in such cases.

The findings at follow-up in the bed-rest series, who were not given prophylaxis, have been compared with those in 73 other patients admitted in later years and treated with six-week courses of A.C.T.H., cortisone, or aspirin and given prophylactic sulphonamide 1 g. daily in hospital and after discharge. Nineteen of the bed-rest cases had recurrences but only five of the drug-treated series. In patients without recurrences there was no difference between the two treatment groups in regard to changes in cardiac status at follow-up. With recurrences, on the other hand, there were marked

differences: recurrences were more common in the bed-rest series (no prophylaxis) and deterioration was common after them, whereas in the treated (prophylactic sulphonamide 1 g. daily) recurrences were uncommon and no one was worse after them.

It is concluded that treatment in hospital with steroid or salicylate has comparatively little influence in most instances on cardiac status at follow-up, but that prophylaxis has a beneficial effect and is the most certain way we have of reducing the morbidity and mortality rate from rheumatic fever.

My thanks are due to Professor E. G. L. Bywaters for much help and advice in the preparation of this paper.

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# PLACE OF RADIOTHERAPY IN TREATMENT OF CANCER OF THE LARYNX*

BY

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There can be no doubt that in the treatment of laryngeal cancer any method that enables the patient to preserve his life and at the same time conserve his larynx must be regarded as the treatment of choice. Radiotherapy alone can do this, and it would seem both humanitarian and in the best traditions of medicine to offer patients this form of treatment wherever possible. It is the purpose of this paper to try to show what radiotherapy can offer. sufferers from cancer of the larynx.

### Clinical Material

During the period 1933-59 some 959 cases of laryngeal cancer were seen at the Royal Marsden Hospital, and the majority of these (807) were referred without any previous treatment having been given (Table I). Much of the material for this study has been

TABLE I.—Cases of Cancer of Larynx, 1933-59

| | |
|---|---|
| Total number of patients seen | 959 |
| Previously untreated cases | 807 |
| Recurrent cases | 85 |
| Post-operative cases | 25 |
| Patients seen but not treated by radiotherapy | 42 |

drawn from the Royal National Throat, Nose and Ear Hospital, and the Metropolitan Ear, Nose and Throat Hospital. Statistically it is important to emphasize that the patients formed a selected group, since they did not include all the cases seen by all members of the staffs at either the Royal Marsden Hospital or its co-operating hospitals. Some of the cases included in the earlier part of this series were treated by my predecessor, Dr. C. A. P. Wood, and in recent years others have been treated by my colleague, Dr. V. M. Dalley.

## Classification

The classical division of laryngeal cancer into intrinsic and extrinsic forms (Isambert, 1876; Krishaber, 1879) —a relic of the early days of laryngology—originally served the simple purpose of separating operable from inoperable tumours. It survived for nearly 90 years, which in itself is a tribute to its value; but the advent of radiotherapy, advances in surgery, and, above all, increased knowledge of the natural history of laryngeal cancer, demonstrated quite clearly that it had served its purpose. This fact received international recognition, and recommendations were made for a new classification of laryngeal cancer for international use (Report, 1959).

Three different forms of tumour arising within the larynx have now been identified. Each form behaves in its own special fashion, has its own prognosis, and often requires a different therapeutic approach. The three types of neoplasm are as follows:

1. *Glottic,* arising from the true vocal cord, the anterior or posterior commissures, and forming the commonest and most favourable tumour.

2. *Subglottic,* arising from the subglottic space; these are the rarest tumours, with a much worse prognosis.

3. *Supraglottic,* arising from the ventricular bands, ventricules, or the root of the epiglottis; these are the most serious of the laryngeal tumours, with the worst prognosis.

In this series of 807 previously untreated cases, 559 tumours (70%) were glottic, 174 (21%) supraglottic, and 73 (9%) subglottic in origin; one was not classified.

## Staging

In addition to classifying cancer of the larynx according to the site of origin of the neoplasm, some attempt was made to group together individual tumours which resembled each other in their extent—that is, tumours were roughly grouped together according to whether they were early or advanced. This grouping together according to the extent of the tumour is termed "staging," and its main purpose is to provide a reliable basis for assessing prognosis and comparing results obtained by different methods of treatment.

The basis of the system in use at the Royal Marsden Hospital (Lederman, 1952) differs in some respects from the proposed international system. In essence, *Stage I* includes the very early cases where the tumour is limited to its tissue of origin, laryngeal mobility is unaffected, and there are no lymph-node metastases; *Stage II* includes the more advanced tumours where local spread has taken place but the larynx is not fixed and lymph nodes are not present; *Stage III* includes tumours accompanied by fixation of the larynx or homolateral lymph-node metastases, or where extralaryngeal spread has occurred; and *Stage IV* includes the very advanced cancers associated with bilateral or fixed lymph-node deposits or distant metastases.

Fig. 1 shows the distribution of the cases according to stage. The trends over the three periods selected indicate that in the second period (1952-6) the percentage of stage I cases was double that of the previous period, and there was a smaller percentage of advanced stage III or IV cases. In the final period the percentage of cases in stage I remained relatively constant, but there was a significant increase in stage II cases—that is, those most suitable for laryngectomy.

Table II shows the value of the classification in relating the site of the tumour to what is possibly the most important single factor in prognosis of squamous cancer anywhere in the head and neck—namely, the frequency of lymph-node metastases.
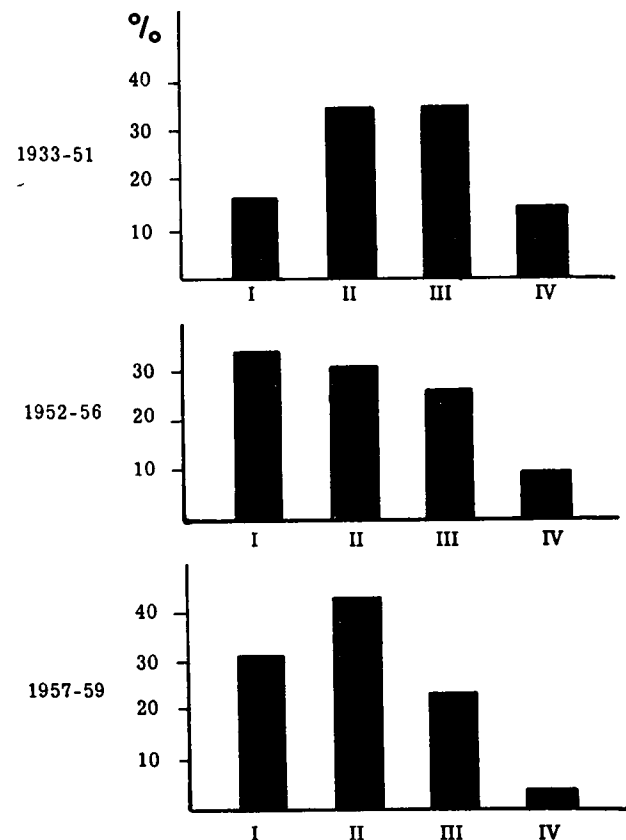


FIG. 1.—New cases treated by radiotherapy. Comparison of stage distribution in three periods.

TABLE II.—*New Cases Treated by Radiotherapy. Incidence of Regional Lymph-node Involvement*

| Site of Tumour | Lymph-node Involvement | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | — | | + | | Bilateral | | |
| | No. | % | No. | % | No. | % | |
| Supraglottic | 114 | 65 | 60 | 35 | 19 | 11 | 174 |
| Glottic .. | 546 | 98 | 13 | 2 | 2 | 0·4 | 559 |
| Subglottic | 66 | 90 | 7 | 10 | — | | 73 |
| Unclassified | 1 | — | — | | — | | 1 |
| Total .. | 727 | 90·1 | 80 | 9·9 | 21 | 2·6 | 807 |

Cancer of the vocal cord is one of the most " benign " cancers, partly because it tends to be slow-growing, but chiefly because of the low risk of metastases. Lymph-node metastasis is almost unknown where a tumour is strictly limited to the vocal cord; it is only when the tumour has spread from the vocal cord that metastases take place, and then only rarely. By contrast the supraglottic tumours metastasize readily and not infrequently to both sides of the neck (Table II): this difference in behaviour is reflected only too obviously in the treatment results (see Fig. 4).

## Age-and-Sex Incidence

Cancer of the larynx is essentially a disease of middle-aged men; only some 7.5% of the patients are women, and the ratio of men to women remained relatively stationary throughout the whole period. It seems to be a curious and unexplained fact that cancer of the head and neck is, with the sole exception of the post-cricoid area, less common and more benign in behaviour

in the female as compared with the male. Table III shows that this may in part be accounted for by the earlier stage at which women seek advice.

TABLE III.—*New Cases Treated by Radiotherapy. Comparison of Male and Female Stage Distribution*

| | Stage I | | Stage II | | Stage III | | Stage IV | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % | |
| Male | 198 | 27 | 262 | 35 | 215 | 29 | 64 | 9 | 739* |
| Female | 23 | 34 | 30 | 45 | 11 | 17 | 3 | 4 | 67 |
| Total | 221 | 28 | 292 | 36 | 226 | 28 | 67 | 8 | 806* |

\* 1 unstaged excluded.

Fig. 2 shows that the mean age for both men and women was approximately 61.2 years. The figures remained relatively unchanged over the whole period. The youngest patient was 25 and the oldest 88: both were males. Apart from the peak incidence in the sixth and seventh decades common to both men and women, the latter were proportionately more affected below the age of 40 and above 80.

When considering the age of patients in relation to tumour site, Fig. 3 shows that the supraglottic tumours tended to occur at an earlier and the subglottic tumours at a later age than the common glottic tumours. The subglottic group also showed a rise in incidence below the age of 40 and above 70: this was probably due to the higher incidence of the tumour in the female (Table IV).
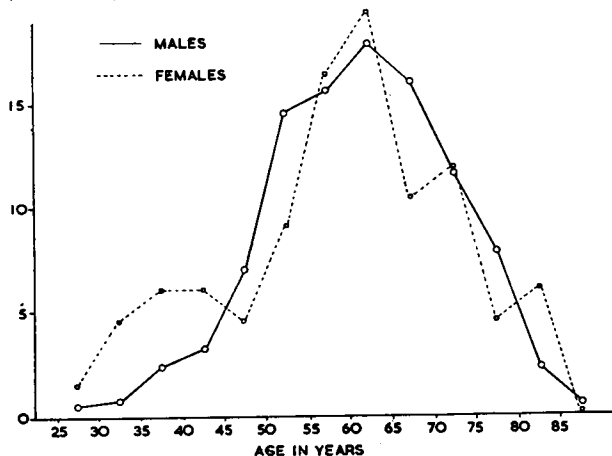


FIG. 2.—New patients treated by radiotherapy. Comparison of proportionate age distributions by sexes.
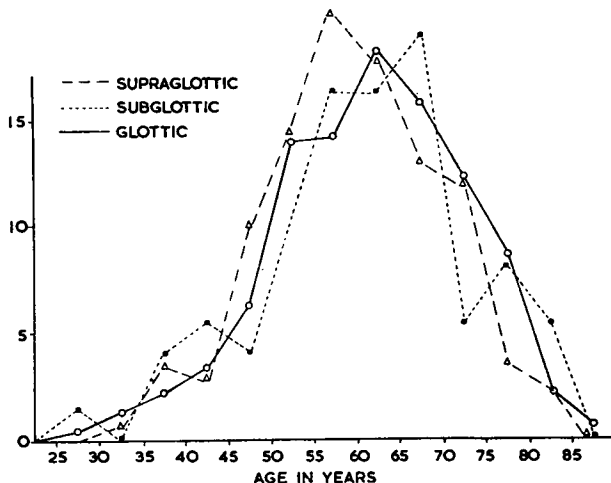


FIG. 3.—New patients treated by radiotherapy. Comparison of proportionate age distributions by site of tumour.

TABLE IV.—*Site Distribution in Relation to Sex*

| | Male | Female | Total |
|---|---|---|---|
| Supraglottic | 161 | 13 | 174 |
| Glottic | 516 | 43 | 559 |
| Subglottic | 63 | 10 | 73 |
| Unclassified | — | 1 | 1 |
| Total | 740 | 67 | 807 |

## Predisposing Factors

*Syphilis.*—Routine serological tests for syphilis were abandoned at the outbreak of the last war and have not been resumed. There is no reason to believe that this disease has any significant relationship to the causation of laryngeal cancer.

*Smoking.*—Our records in relation to the smoking habits of patients were incomplete, since in the early years covered by this report the possible relationship between cancer of the respiratory tract and tobacco was not appreciated, and so our records covered only the more recent years after this possibility had come to the fore. We can only offer a negative observation— namely, that it is most unusual to encounter laryngeal cancer, particularly vocal-cord cancer, in the non-smoking male. Such few non-smokers as were seen were mostly women suffering from subglottic cancer.

*Vocal Abuse.*—Among our patients there were many whose livelihood depended on their voice—that is, parsons, actors, singers—but again there is no evidence to show that these people are more likely to develop laryngeal cancer than those in other occupations where use of the voice is not so dominant.

*Pre-malignant Lesions* (Lederman, 1961).—A previous history of papilloma, leucoplakia, or keratosis was occasionally encountered: because our material was selected and the patients with these lesions were referred for treatment after the development of malignancy it was impossible to determine the frequency with which this change occurred. Premalignant lesions were not treated by radiotherapy for the following reasons. (1) There was no certainty that malignancy would supervene in any given case, and, even if it should, the time interval might be very long. (2) Pre-malignant lesions are not particularly radiosensitive and full doses of radiation would have had to be given with all its attendant discomforts and risks (Report, 1959). There was, moreover, no guarantee that even when apparently successfully treated by radiation recurrence might not later take place and malignancy then supervene, in which event the patient would be worse off, since in these circumstances he would be debarred from further use of radiation at a time when he might most need it.

## Treatment Policy

Since early laryngeal cancer can be treated successfully by both radiotherapy and surgery, these are to be regarded as competitive methods. The advantages of radiotherapy are, however, so overwhelming that they cannot, or should not, be ignored. These particular advantages are: (1) avoidance of an operation, (2) preservation of a normal voice, and (3) the patient is given two chances of survival. If the patient submits to surgery first and recurrence takes place, the radiotherapist can do very little for him, since the post-operative irradiation of cancer cells in scar tissue is rarely of value.

In this series all early cases in stage I and II—that is, those without laryngeal fixation and unaccompanied by lymph-node metastases—received radiotherapy without any equivocation. The presence of some associated pre-malignant condition such as leucoplakia or keratosis may add to the technical difficulties of treatment and reduce the prognosis with radiotherapy, but these complicating conditions should not be regarded as an excuse for advocating surgery in preference to radiotherapy, since the latter may still prove successful and the patient's larynx thereby be spared.

For the advanced case there should be little competition between the surgeon and the radiotherapist. Surgery is certainly the mainstay of treatment for the following cases: (1) stage III and IV cases, particularly when complicated by laryngeal fixation, lymph-node metastases, or perichondritis; and (2) for recurrent cases after previous conservative surgery or radiotherapy.

The prognosis by any method of treatment for these advanced cases is not very good and we believe a preliminary course of radiation to be of value. The chief advantages of this combination are: (1) a small number of tumours, particularly in stage III, proved radiosensitive and the need for operation did not arise (see Fig. 9); (2) a preliminary course of radiotherapy caused the growth to shrink and could bring a doubtfully operable tumour into the bounds of operability; (3) it enabled the extent of an operation to be reduced —for example, if a pharyngeal extension regressed under radiotherapy the subsequent operation could be limited to laryngectomy instead of pharyngolaryngectomy; and (4) the incidence of recurrences in the tracheostome, particularly in the subglottic group, could be reduced by preliminary irradiation of the whole of the cervical trachea.

Extensive inoperable tumours, particularly in elderly patients, were treated by palliative radiotherapy alone; but the advanced age of the patients was never used as an argument against the routine employment of radiotherapy if the tumour was early.

A six-weeks period was allowed to elapse between the end of the treatment and the assessment of its success or failure. If at the end of this period the larynx was normal the patient was followed up regularly; if the larynx had not returned to normal and there was persistent ulceration, residual infiltration, or fixation, then a direct examination was performed and a biopsy specimen taken only from a frankly tumorous or suspicious area. If, on direct examination, the mucosa was found to be intact and there was no suspicious area, biopsy was not performed, since this procedure might, by destroying the integrity of the mucous membrane, facilitate infection and provoke perichondritis. If the biopsy was positive laryngectomy was performed with the minimum of delay.

In the more advanced cases it was sometimes difficult to reach a definite decision since the larynx might look suspicious, and ulceration, fixation, and oedema might be present, but biopsy might be repeatedly negative. We believe it is justifiable in these cases to advise laryngectomy, as, in our experience, advanced cases which do not present a reasonably normal appearance after radiotherapy are rarely cured; to await a positive biopsy very often means waiting too long and the patient could forfeit his chance of cure by surgery. Where laryngectomy has been performed in these circumstances it is rare not to find cancer cells in the operative

specimen. The timing of the surgery in relation to the radiotherapy was important. The interval of six weeks after the termination of treatment was chosen, partly because at the end of this time it could be assumed that the maximum tumour regression in response to the radiation had occurred; and, more important still, if the treatment failed there was less chance that during a laryngectomy performed between 6 and 12 weeks after radiation tissue fibrosis, troublesome bleeding, and delayed healing would be encountered to the same extent as would have been the case if the operation was performed after the third month when the post-radiation changes likely to cause these difficulties had become firmly established (Mill, 1956; Ormerod and Shaw, 1956).

## Preparation and Care of the Patient

Patients in good general condition with early carcinomas required little preparatory treatment. A routine blood count and radiographic examination of the larynx and chest were undertaken. A Wassermann test was done only if there was a history of syphilitic infection or clinical features suggested that possibility.

The routine radiographic procedures were thought to be of prime importance, since soft-tissue radiography (lateral view and tomography) provided a great deal of information that could not be obtained by purely clinical or instrumental measures. The routine examination of the chest was also performed to exclude pulmonary tuberculosis, to detect other pulmonary infectious complications, and to ensure that the patient had not a further primary neoplasm of the bronchus.

A preliminary biopsy was routinely performed except where a patient had such severe respiratory obstruction that the trauma of biopsy might have precipitated tracheotomy. Occasionally in the very frail or senile patient this procedure was not insisted upon. It is of the utmost importance that a preliminary tracheotomy be avoided if the patient is to receive benefit from a course of radiotherapy. The patient with respiratory obstruction unless *in extremis* was given prompt radiotherapy and by this means tracheotomy was usually avoided. Once a tracheotomy was performed the technique of treatment became more complicated and the prognosis worse (Table V).

TABLE V.—*Tracheotomy in Relation to Radiotherapy. Fifty-two Operations*

| Site | Before Radiotherapy | During Radiotherapy | After Radiotherapy |
|---|---|---|---|
| Supraglottic | 3 | 4 | 7 |
| Survival | None at 5 years | None at 5 years | None at 5 years |
| Glottic | 12 | 3 | 15 |
| Survival | 2 at 5 years | None at 5 years | 3 at 5 years |
| Subglottic | 6 | 1 | 1 |
| Survival | None at 5 years | None at 5 years | None at 5 years |
| Stage | All cases Stage III or IV | All cases Stage III | 21 cases Stage III and IV, 1 Stage I, 1 Stage II |

Apart from the cases where biopsy was omitted, it occasionally happened that a biopsy specimen, even when taken, was subsequently found to be inadequate, negative, or unsatisfactory. An attempt was made to repeat this operation if there was clinical doubt concerning the diagnosis, but where no such doubt existed and if the patient had already started radiation treatment it was thought to be unwise to repeat the procedure. Table VI shows the different histological varieties of tumour encountered and also the number of patients for whom no histological confirmation of the diagnosis

TABLE VI.—*Previously Untreated Patients Treated by Radio-therapy (1933–59) Classified According to Histology*

| | |
|---|---|
| Squamous-cell carcinoma and carcinoma not otherwise specified | 608 |
| Carcinoma specified as poorly differentiated, undifferentiated, or anaplastic | 77 |
| Carcinoma *in situ* | 66 |
| Adenocarcinoma | 1 |
| Unconfirmed | 52 |
| Other malignant tumours | 3 |
| | 807 |

was available: the accuracy of the clinical diagnosis was, however, borne out by the results, since most of them died of cancer (see Fig. 7).

The problem of the teeth required consideration, and septic teeth were removed even when not within the field of radiation. The smoking and drinking habits of the patient were not curtailed to such an extent that he was made miserable. He was advised to give up smoking, but, if he did not wish to do so, smoking was restricted to the postprandial cigarette, pipe, or cigar. Equally, drinking habits were controlled ; alcohol in the form of spirits was forbidden, but beer or wine was permitted. Fit patients who lived near the treatment centre were not admitted to hospital and most of them had treatment as out-patients, though some required admission for the terminal part. The attitude towards working depended upon the patient's temperament and job. In principle, we found that the patient was a happier and more contented person the less his normal routine life was disrupted. The following people, however, were admitted to hospital: the elderly, the debilitated or sick patients, those with advanced disease, and those living far from the treatment centre.

Patients with tuberculosis or other respiratory diseases tolerated radiation well but were usually admitted, and those presenting with stridor or respiratory obstruction were always admitted as emergencies. If, as should be the case, the patient's larynx was to be examined very often during radiation treatment, the difficult subject was taught how to " show his larynx." It was most exceptional to find individuals who did not respond to patient and correct instruction. Resort to regular cocainization was practically never necessary.

## Technique of Treatment

The technique of treatment depended on the age, general condition of the patient, and the site, histology, and extent of the tumour. A haemoglobin of 60% was regarded as the lowest limit for radiotherapy: below this level a blood transfusion was given.

All early cases of laryngeal cancer were treated by telecurie therapy and we had at our disposal a variety of specially designed head and neck units containing radium, cobalt, and, more recently, radioactive caesium. X-ray therapy at conventional voltages was reserved for the palliative treatment of advanced or recurrent cases. In telecurie therapy a protracted fractionated system of dosage was used: a dose of 300 r a day was given to one or two fields for five or six days a week, the total tumour dose varying from 5,500 to 8,000 r in six to eight weeks.

## Post-radiation Complications and Sequelae

Under modern conditions with present-day equipment technique and knowledge of dosage, post-radiation complications should rarely be encountered and severe damage such as radio-necrosis never at all.

There were four main post-radiation complications that haunted the radiotherapist in the past : (1) laryngeal

oedema, often severe enough to require tracheotomy : (2) perichondritis ; (3) cartilage necrosis ; and (4) changes in the irradiated skin. In this series of patients these complications were prevented by attention to the following factors.

*Selection of Case.*—The advanced cases of cancer of the larynx were always associated with malignant perichondritis and most of these patients ultimately required surgery. If preliminary radiotherapy was decided upon, then, bearing in mind that its purpose was largely pre-operative rather than curative, the daily dose, the overall treatment time, and dosage were selected so as not to aggravate the already existing perichondritis. The use of antibiotics helped considerably in cases of this kind. If the perichondritis could not be controlled there was little point in persevering with radiotherapy, and if the lesion was operable the patient was submitted to operation without delay.

*Selection of Apparatus.*—Gamma-radiation was considered preferable to conventional 200-kV x-radiation.

*Control of Radiation Reactions.*—Radiation treatment had to be adapted to the patient and his tumour. This could be achieved by attention to daily and overall dosage and the total time over which the treatment was spread. Extending treatment over a minimum period of six weeks resulted in a comfortable patient and generally the patient who did not suffer during treatment rarely encountered complications after treatment.

Among the patients in this study the incidence of post-radiation complications was very small. Tracheotomy for radiation oedema during treatment was almost unknown, and if it did become necessary it was nearly always regarded as being the fault of the radiotherapist. Post-radiation tracheotomy, with very rare exception, was due to failure to control the disease. There were only two cases of skin necrosis in this whole series, and for the past 10 years the skin changes during radiation therapy were restricted to a mild dry desquamation, and post-radiation subcutaneous fibrosis or telangiectasis was not encountered. Persistent localized laryngeal oedema were occasionally seen when high dosage had to be given, and were found particularly among the supraglottic group of tumours. A mild perichondritis as evidenced by localized tenderness and oedema of the larynx and homolateral earache was also occasionally encountered, usually after a history of respiratory infection. It responded well to voice-rest and treatment by antibiotics. Necrosis of the endolaryngeal soft tissues was extremely rare.

## Results of Treatment

In dealing with a disease such as cancer, for which no certain remedy exists, it is easy to become a partisan of a particular method of treatment. In order to avoid this very human weakness statements concerning treatment policy must be based upon the evidence provided by treatment results. Radiation techniques or surgical operations designed for the curative treatment of malignant disease do not merit serious consideration unless they are supported by results. Figs. 4–7 show the results achieved by our policy of irradiation as the method of choice with surgery reserved for failures.

All results reported here are quoted as crude survival rates. Patients who were lost to follow-up and those who died from intercurrent disease were counted as died of cancer. As many of our patients were elderly and many came from foreign countries where the importance

C

of follow-up is seldom appreciated, these cases represented a serious statistical liability.

There was a further loading against radiotherapy because of the epoch covered by this report—namely, the pre-laryngectomy and pre-antibiotic era, when the Royal Cancer Hospital, as it was then known, was almost a home for the dying and patients were admitted moribund and given perhaps one or two radiation treatments before expiring: yet these patients, nevertheless, were included.

The influence of site, stage, and sex is shown in Figs. 4, 5, and 6. The significantly better results in women are well shown, as is also the marked influence of stage upon results. So long as the larynx remained mobile and lymph nodes were absent, the prognosis was very good even at 10 years. The advanced cancers in stage III and IV were cured in only a minority of cases whatever was done. Although it was exceptional to see any tumour other than an epithelioma, the differences in results at five years between the differentiated and undifferentiated epitheliomata were noteworthy (Fig. 7). The excellent prognosis of patients with "carcinoma in situ" is well shown.

Figs. 4–7 give the results obtained without reference to the precise method of treatment. Table VII, based on the stage of the disease, illustrates the part that

laryngectomy plays in relation to radiotherapy. Some 70% of the patients, whose radiation treatment was unsuccessful, came to surgery within the first year after treatment: only a very small proportion (4%) of patients required laryngectomy for recurrence after the third year. The need for laryngectomy was least in stage I (13.6%) and highest in stage III (34.5%). Only a minority of stage IV cases ever merited the attempt at laryngectomy.

Some 22% of all patients treated had to undergo post-radiation laryngectomy: in approximately a similar percentage of the survivors after three and five years the

TABLE VII.—*Laryngectomy after Radiotherapy* (1933–56)

| Stage | Total No. of Cases | Total No. Undergoing Operation | Time Elapsing | |
|---|---|---|---|---|
| | | | Within 1 Year of Radiotherapy | After 3 Years |
| I | 139 | 19 (13·6%) | 11 | 2 |
| II | 181 | 37 (20·4%) | 23 | 2 |
| III | 165 | 57 (34·5%) | 44 | 1 |
| IV | 61 | 10 (18%) | 9 | — |
| | 546 | 123 (22·5%) | 87 (70·7%) | 5 (4%) |

Of these 546 patients, 326 (60%) survived three years: 68 (21·5%) after laryngectomy. At five years 190 (48%) of 395 patients survived: 44 (23·1%) after laryngectomy.
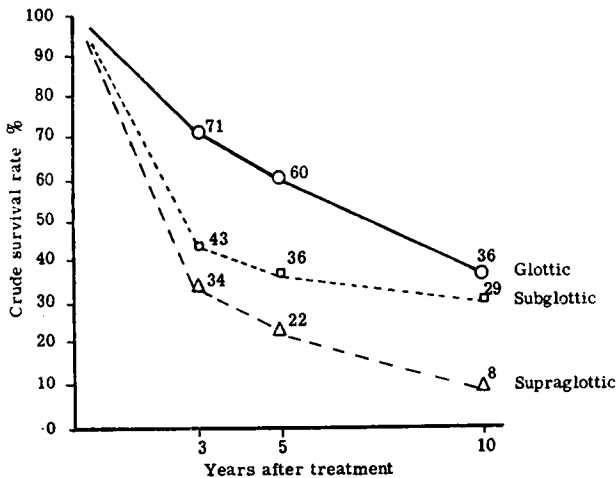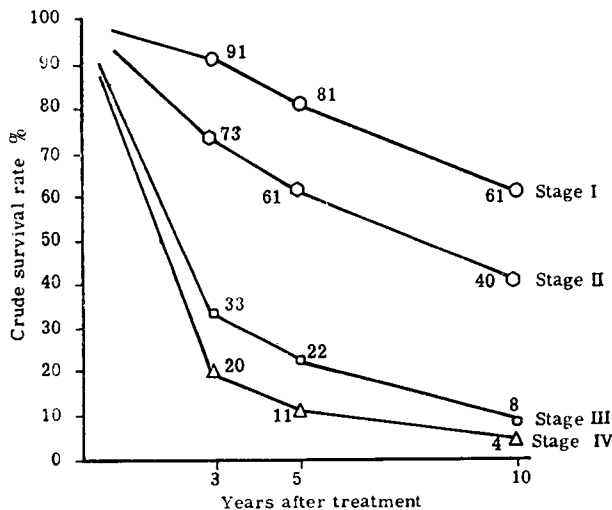


FIG. 4.—Results according to site of tumour.



FIG. 6.—Results according to sex.
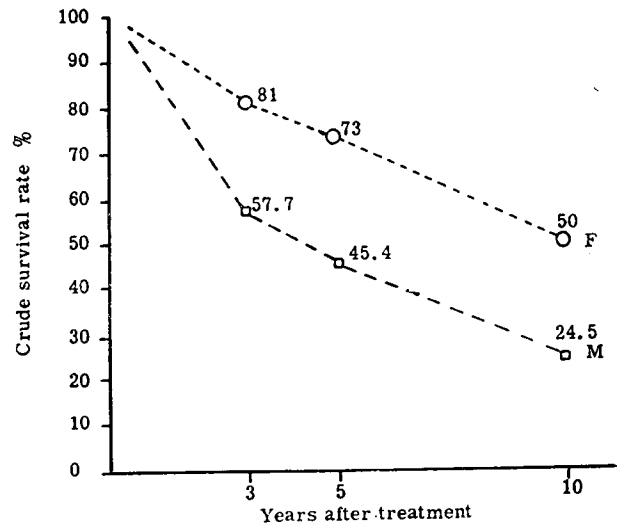


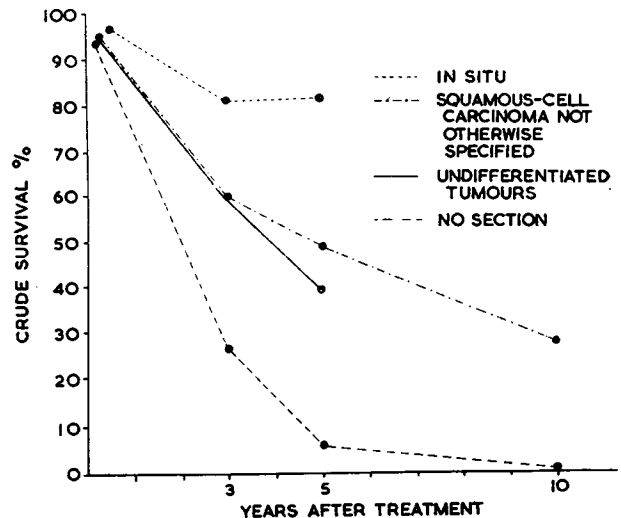FIG. 5.—New cases treated by radiotherapy. Results according to stage.



FIG. 7.—Results according to histology.

larynx had to be sacrificed. The outstanding achievement of radiotherapy lay in the fact that nearly four-fifths of the survivors retained the larynx.

Fig. 8 shows the results in relation to site and laryngectomy. Again it can be seen that the majority of survivors retained the larynx whatever the site of origin of the tumour, and in this connexion the results obtained in the subglottic group are of interest. This is the rarest of the laryngeal tumours and the one to which the surgeon lays claim on the alleged grounds that they are insensitive to radiation. From the results shown in Fig. 8 there is no doubt that some subglottic carcinomas were curable by radiotherapy, and they were generally the tumours in women, situated in the anterior half of the subglottic space, the vocal cords remaining mobile and nodes being absent.

Supraglottic cancers are the most deadly of the laryngeal cancers, chiefly because of the lymph-node



FIG. 8.—New patients treated by radiotherapy. Three-year crude survival rates (1933–56) and five-year crude survival rates (1933–54) by site, showing the number of patients requiring laryngectomy after radiotherapy.



FIG. 9.—New patients treated by radiotherapy. Five-year crude survival rates (1933–54) by stage, showing the number of patients requiring laryngectomy after radiotherapy.

problem, but also because they are situated in a part of the larynx where the pre-epiglottic space and the laryngeal cartilages are most readily invaded. Radiotherapy was the main hope for these patients, with surgery very much in the background.

Fig. 9 shows the results in relation to stage and laryngectomy. In stages I and II only a small proportion of the survivors had to sacrifice the larynx, whereas in stages III and IV the survivors were few and approximately half owed their survival to laryngectomy.

### Conclusions

All cases of early or moderately advanced laryngeal cancer ordinarily regarded as suitable for laryngo-fissure or laryngectomy should be treated by radiotherapy for preference, since the results obtained by this method are good and the functional result is as a rule excellent.

Radiotherapy is only occasionally successful in the treatment of advanced cases of laryngeal cancer, and surgery must be regarded as the mainstay of treatment. Until such time as more statistical information is forthcoming concerning the value of surgery alone for this group of cases, a preliminary course of radiotherapy has much to commend it.

Incomplete operations for advanced laryngeal cancer are inexcusable, and to send such patients to the radiotherapist in the hope that post-operative radiotherapy will succeed where surgery has failed betokens a faith in radiotherapy that cannot be justified.

Some subglottic cancers can be cured by radiotherapy: and those that cannot may yet benefit from pre-operative irradiation, since the risk of recurrence in the tracheostome may be reduced.

The supraglottic lesions are the most serious of laryngeal cancers. The early cases can be cured by radiotherapy alone, but the advanced cases with lymph-node metastases are only exceptionally cured by any combination of methods.

In the series of cases reported here, approximately one in five of the patients required laryngectomy after radiotherapy; of the patients surviving three and five years, four out of five retained the larynx.

### Summary

During the period 1933–59 a total of 959 cases of laryngeal cancer were seen at the Royal Marsden Hospital, 807 being previously untreated. The primary tumour was glottic in 70% of the cases, supraglottic in 21%, and subglottic in 9%. The average age of the patients was 61.2 years, and 7.5% were women. No special predisposing cause was apparent, although it is unusual to see laryngeal cancer in non-smokers.

The treatment adopted was telecurietherapy, using gamma radiation from a radium and more recently from a cobalt source. X-ray therapy was employed only for palliation. Surgery was reserved for radiation recurrences or failures, the success or failure of treatment being assessed within six weeks of its termination. Post-radiation damage was rarely encountered, nor was any subsequent surgery hampered by the preceding radiotherapy.

The three-year and five-year survival rates for all patients was 60% and 48% respectively; among the former 21.5% of the patients had undergone laryngectomy after radiotherapy, and among the latter 23.1%.
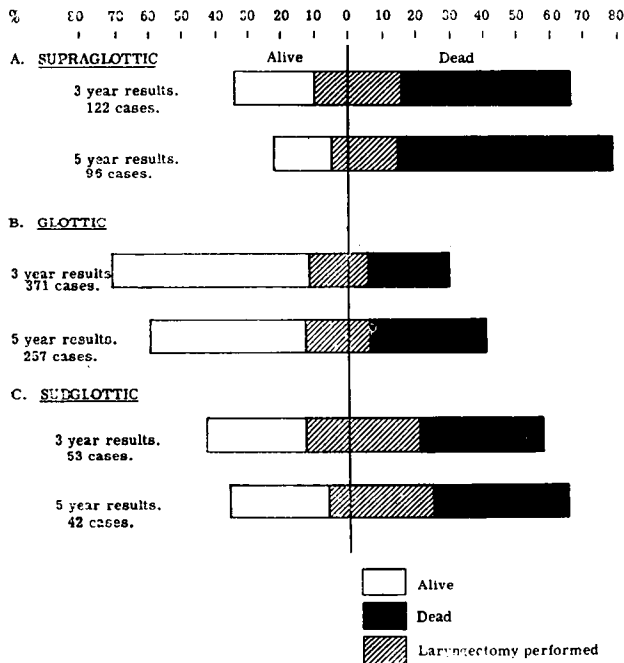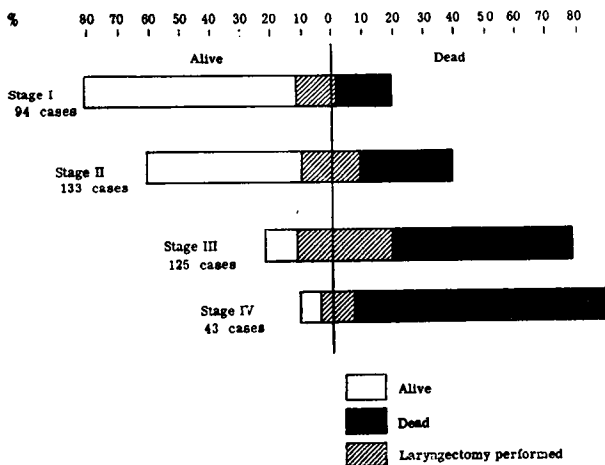
I am indebted to my colleagues at the Royal Marsden Hospital and its co-operating hospitals for referring the patients. I thank Dr. Robert S. Stone and Dr. Franz Buschke, of the radiation therapy department of the University of California Hospital, San Francisco, and Dr. Donn Mosser, director of the radiation therapy department of the University of Minnesota Hospital, Minneapolis, for permission to draw upon material used for the first Low Beer Memorial Lecture and the fifteenth Leo Rigler Lecture respectively. Dr. Henry Stratton, of Messrs. Grune and Stratton, has kindly given me permission to use material which has been already incorporated in my forthcoming book on cancer of the larynx and laryngopharynx. Finally, I wish to thank my secretary, Miss Morehead, for the preparation of the manuscript, and Mr. Payne, statistician to the Royal Marsden Hospital, for providing the tables and figures.

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# INCIDENCE AND AETIOLOGY OF THYROID CARCINOMA

BY

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The reported incidence of thyroid carcinoma, even when calculated on material gleaned from similar populations, shows marked discrepancies and has given rise to widely contrasting opinions regarding its importance as a cause of death. Likewise, opinions differ on the incidence of malignant change in surgical material, particularly when consideration is given to non-toxic nodular goitre. This is due to the fact that such figures depend upon the policy of the surgeon, the type of centre from which they are reported, and the histological criteria used in the diagnosis of malignancy.

Furthermore, during the past decade the potential carcinogenic effects of the therapeutic use of irradiation to the cervical region and of antithyroid drugs for benign thyroid states has often been a matter of speculation.

Northern Ireland, with a relatively stable population and readily accessible material, was regarded as ideal for a study of the incidence and possible aetiological factors of thyroid carcinoma in man because it is possible to include all surgical cases from both urban and rural hospitals, thus avoiding the selective factor which influences reports from centres specializing in thyroid disease.

## Material

Most of the material (Table I) used in this study includes those cases in which the diagnosis was made by histological examination over a 25-year period (1934–58) in the department of pathology, the Queen's University of Belfast, and a four-year period (1955–8) in the laboratories of Belfast City Hospital. Special reference is made in the text when additional cases are included. All surgical specimens from the whole of

TABLE I.—*Source, Period of Observation, and Pathological Diagnosis of Surgical Thyroid Specimens*

|  | University Department (1934–58) | Laboratories, B.C.H. (1955–8) |
|---|---|---|
| Non-toxic solitary nodular goitres .. | 658 | 173 |
|     ,, multiple ,, | 728 | 211 |
| Total non-toxic nodular goitres | 1,386 | 384 |
| Primary hyperthyroidism .. | 899 | 219 |
| Secondary ,, .. .. .. | 178 | 39 |
| Primary carcinoma .. .. | 122 | 27 |
| Hashimoto's disease .. .. .. | 49 | 12 |
| Miscellaneous .. .. .. .. | 252 | 23 |
| Total .. .. .. | 2,886 | 704 |

Northern Ireland are submitted to one or other of these two departments.

In all cases representative sections were available for review. The criteria of malignancy used in this study are the same as those generally applied to cancer of all other organs. These include changes in cell type and staining reactions, aberrant nuclear forms and hyperchromatism, increased mitotic activity, loss of organoid pattern, capsular, lymphatic, or venous invasion, and finally metastases.

However, in some tumours the morphological changes were thought to be insufficient and the diagnosis of malignant change could be made with certainty only by demonstrating invasion or metastases. Such tumours included encapsulated and well-differentiated ones and those removed from patients who had received antithyroid therapy prior to operation.

The information concerning the use of irradiation and antithyroid drugs for thyroid disease before the diagnosis of malignant change was collected either by personal interrogation of the patients or indirectly by a questionary sent to consultants and general practitioners who had at any time seen the patients. That regarding a history of thyrotoxicosis was obtained by an examination of the case-notes recorded by the physicians or surgeons.

## Incidence

*Necropsy Material.*—In this study thyroid cancer was encountered on 15 occasions in 15,100 necropsies. This incidence of 0.1% agrees with that reported by Wilson (1921) for the United States, Zimmerman *et al.* (1950), and Steiner (1950), but differs from that recorded by Vanderlaan (1947), who could find only five cases of thyroid malignancy in 18,668 necropsies.

*Registrar-General's Records.* — The figures for Northern Ireland are shown in Table II. During a three-year period (1955–7 inclusive) the cause of death

TABLE II.—*Statistics Reported by the Registrar-General for Northern Ireland*

|  | 1955 | 1956 | 1957 | Average |
|---|---|---|---|---|
| Total deaths due to all types of cancer .. | 2,170 | 2,201 | 2,306 | 2,228 |
| Deaths due to thyroid cancer | 14 | 16 | 11 | 14 |
| Percentage of all cancer deaths due to thyroid cancer .. .. .. | 0·6 | 0·7 | 0·5 | 0·6 |

was attributed to carcinoma of the thyroid gland in 14, 16, and 11 cases respectively. Taking the average figure for the three years, thyroid cancer accounted for 0.6% of all cancer deaths.

*Surgical Material.*—The frequency with which thyroid cancer occurs in surgical material is shown in Table III.