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TREATMENT OF CANCER OF THE LARYNX BY INTERSTITIAL RADIUM NEEDLES

BY

W. DOUGLAS HARMER, M.C., F.R.C.S.

Consulting Surgeon to the Throat Department, St. Bartholomew's Hospital; Consulting Surgeon to Mount Vernon Hospital and the Radium Institute

The object of this investigation was to ascertain the value of interstitial radium needles in the treatment of cancer of the larynx and to compare it with other methods. This subject has not received as much attention as it deserves. Since 1924 120 patients have had operations with the help and advice of colleagues in the cancer departments of St. Bartholomew's Hospital, Mount Vernon Hospital, and the Radium Institute.

In so limited a space it is not possible to name all the "happy band of brothers," but I am especially indebted to Finzi for suggesting that the method should be tried, to Stanford Cade for his valuable advice and co-operation during at least 20 years, and to a number of distinguished physicists, particularly Gray and Neary, who have planned the method of delivering the best dose to the different parts of the larynx, and lastly to my son, who has helped me in the preparation of this paper.

All these patients have been followed up, with the exception of two who left the country within a few months of their treatment and who have been omitted: in one the growth had already disappeared, so that the outlook was favourable, and the other, with an advanced growth, has been assumed to have died of cancer.

Up-to-date reports of all these are recorded. A few that were lost after five years have been listed to the date of their last record.

Clinical Features

Before describing details of treatments some remarks about these cancers are advisable.

Aetiology.—Cancer of the larynx occurs chiefly in males (only 13% in females). Most of our patients were between the ages of 50 and 65. The oldest was 78; the youngest 20. During 55 years in practice I know of only one earlier case—that of a boy of 9½, seen recently in consultation with Mr. James Crooks, who performed a laryngo-fissure and who has since published this interesting case, which I have not included in my series. Nothing was discovered about causation, but a number of these patients stated that their symptoms started after influenza, and one young woman, who was apparently cured by radium needles for two years, had a rapid recurrence following a pregnancy and died in six months. Normally intrinsic cancer grows slowly, but the rate of growth is quite unpredictable. Thus, a

patient from India with hoarseness for about a month had a small localized lesion like a simple wart. As the section showed carcinoma he was treated by laryngofissure and the whole of his vocal cord was removed. His wife was assured that the outlook was excellent. In a short time, however, it became obvious that the disease had not been arrested, and he died six months later with large metastases in the cervical lymph nodes. The same may happen with growths elsewhere in the throat. A doctor had a small pedunculated wart the size of a pea on his tongue which looked like a simple papilloma. The biopsy report stated, "No evidence of carcinoma." Bilateral metastases were noted soon afterwards and grew rapidly, and when he died in six months they were as large as hens' eggs. Small pedunculated lesions in the upper air passages may be very malignant and incurable.

Symptoms.—It has long been accepted that the shorter the history of hoarseness the better the outlook, but, strangely enough, this statement is not always reliable. Table I gives the histories in 89 patients. It shows sur-

TABLE I.—Length of History

	Months				Years									
	<3	3	6	9	1	2	3	4	5	7	10	15		
No. of cases	2	19	15	11	11	16	6	4	1	2	1	1		
3-year survivals	0	11	6	5	5	7	2	2	0	0	0	1		

prisingly little variation in survivals after three months. Although the numbers are small it is still not clear why this should be so. It seems that the outlook depends more on situation, type of lesion, and resistance to cancer. A man with a short history may be more difficult to cure than another who has had trouble for years. Incidentally, people who have lived in the Tropics for many years, who have led a sedentary life, or who have eaten and drunk too much seldom survive for long. On the other hand, another patient with 15 years' hoarseness and a very extensive growth involving the cartilages on both sides was needled and lived free of disease for 10 years. Presumably, a patient's resistance to cancer may be lower at the beginning of the disease than after a number of years. Whatever the explanation, some patients respond surprisingly well and others put up no fight at all.

Situation.—It is not known why cancer in one part of the larynx can be cured so easily whereas with a similar growth in another place a patient rarely survives for long. A good instance is cancer of the epiglottis: on the tip it may be so comparatively innocent that it can safely be treated with transoral diathermy excision, while on the base it is a dangerously malignant cancer which can seldom be cured even by wide laryngectomy. It is therefore enormously important to know how the disease behaves in different situations.

Biopsy.—This should always be made, and be repeated if necessary. The report may be negative. Several of our patients required three or more biopsies. If the disease is clinically malignant it should be treated as such. No patients had sarcoma, and personally I have seen only two cases. Generally speaking, the low-grade cancer has the best prognosis, but in the larynx the situation is more important than the histology. Most of our cases had biopsies. Many years after needling, Dr. Ruth Pearson examined the sections of 48 patients at my request and attempted to foretell the outcome according to Broders's grading. The results are expressed in Table II, which appears to show that, contrary to present-day opinion, grading is of considerable value.

TABLE II

	No. of Cases	Clinical Stage		Outcome	
		Early	Advanced	Lived or Died Free of Cancer	Died of Cancer
Broders's stages 1 and 2	24	6	18	15	9
" " 3 " 4	24	5	19	9	15

Clinical Stages

There are three main stages :

I. Early Intrinsic

(37 patients—31% of total reported.) Here the lesion is strictly confined inside the cavity of the larynx. It is usually a small, slowly growing warty lesion localized to the anterior part of the vocal cord and occasionally spreading to the anterior commissure or to the opposite cord. It involves the mucous membrane only, and can often be

FIG. 1.—Stage I. Early intrinsic.

stripped off without damaging the muscles of the cord (Fig. 1). In fact, when doing a biopsy it is important not to bite too deeply for fear of making a notch which may damage the voice permanently. In rare cases a growth may be hard and ulcerated, which is a more serious condition. If the lesion extends below the cord it is no longer a stage I type. Early lesions often grow slowly and have long histories of hoarseness. They never invade the cervical lymph nodes. At least 80% are curable.

II. Advanced Intrinsic

(72 patients—62% of total reported.) When first examined these growths are nearly all very advanced, but without enlarged nodes. Incidentally, it is extremely difficult to decide how localized they are, particularly when the cord is immobile. Usually the whole vocal cord is involved and the lesion sometimes spreads to the anterior commissure, the base of the epiglottis, the arytenoid or subglottic space (Fig. 2). Sixty were unilateral, while twelve of them had bilateral lesions which had spread across the anterior or, rarely, the posterior commissures. Eight of these had

no tenderness or external swelling, but, when exposed, the growths had perforated the membranes and invaded or softened the cartilages, usually at the lower border of the thyroid cartilage or through the crico-thyroid membrane. Only one of them was cured for six years. Fig. 3 shows such a case in which a localized lesion which seemed superficial was found at operation to have penetrated the cartilage and so could not be included in stage II.

Clinically, there are two groups which help to decide the treatment. (a) The large, soft, cauliflower, non-ulcerated type, with a freely movable vocal cord and therefore no deep infiltration. Radium needling should be tried before laryngectomy. Thirty-three patients were treated, many with good results. (b) The hard, nodular, ulcerated type with a fixed cord, which signifies deep extension of the disease. Without operation it is impossible to determine how serious this is, but 39 were deliberately treated and some of them were cured. Nearly all these lesions were temporarily improved, and the ulceration usually disappeared.

FIG. 2.—Stage II. Advanced intrinsic.

FIG. 3.—Apparently intrinsic (stage II) found at operation to be perforating thyroid cartilage (stage III).

The neck should always be examined to ascertain if there is any external swelling or thickening of the larynx. If on firm pressure the patient complains of tenderness or pain on the affected side, perichondritis should be suspected.

III. Extrinsic

(9 patients—7% of total reported.) Here the lesion is no longer confined inside the larynx. Two different types must be included.

(a) The growth which starts in the larynx and then spreads upwards to the base of the epiglottis or tongue or over the lateral fold to involve the pharynx or pyriform fossa, below the vocal cord to the subglottic space or trachea, posteriorly to the arytenoid cartilage or to the post-cricoid region (Fig. 4). All such cancers progress rapidly, and these patients seldom survive for more than a year if untreated.

FIG. 4.—Extrinsic (stage III).

(b) Here the cancer starts either on the margin of the larynx or on the neighbouring part of the pharynx, spreading later into the larynx.

In the 1945 annual report of the B.E.C.C. dealing with extensive cancer of the larynx, the site of origin was given as follows :

Pyriform fossa	males	137	..	females	12
Post-cricoid space	"	22	..	"	68
Aryepiglottic fold	"	42	..	"	4
Vallecula and epiglottis	"	61	..	"	4

Such growths are always very malignant and progress rapidly, and the patients rarely live (untreated) for as much as a year. Involvement of the lymphatic nodes is common. The same report described : no nodes, 49 ; enlarged nodes, 81 ; nodes and adjacent tissues involved, 244 ; distant metastases, 9. To emphasize their virulence it was stated that, in spite of treatment, chiefly irradiation, only 15 cases survived for five years. With modern treatments much better results are now obtained.

Choice of Treatment

These can be considered historically. The first attempt to cure cancer was naturally by surgery.

Laryngectomy

In 1863 the first laryngectomy for papillomata was performed by Sands (Canada) ; in 1866 Patrick Watson (Edinburgh) removed a larynx for syphilis ; and in 1873 Czerney and Billroth performed another laryngectomy for cancer. In 1887 the German Crown Prince contracted cancer, and von Bergmann advised this operation. When pressed, this great surgeon said that he had performed it seven times, with an average survival of 19 days. His advice was not accepted. But the prince's illness caused enormous controversy and Queen Victoria sent Morell Mackenzie to advise her son-in-law, greatly to the annoyance of the German surgeons, who walked out. The prince lived for just under a year, long enough to become emperor.

The years 1870 to 1900 can be described as the age of laryngectomy. During this period many larynges were removed, but nearly all the patients died of bronchopneumonia, sepsis, and heart failure. With antibiotics and modern anaesthesia laryngectomy can now be safely performed by surgeons who have sufficient experience of this operation. The mortality should be 2 to 3% provided the general health of the patient is good. It has always been a popular operation for all stages of the disease, and it is still regarded by many surgeons as preferable to other methods, particularly in Europe and America. But it is still a difficult operation for general surgeons, and for the patient is a great handicap. No patient should be told that it is the only safe treatment ; nor can it be pretended that it will make no difference, for it often causes great depression. The patient should realize that only about 15% of them get good voices.

To-day there are simpler treatments which can safely be tried first. Without doubt laryngectomy is quite unnecessary for early lesions ; before long it may even be found that radiotherapy in some form may cure a number of advanced cancers, and it will not be surprising if pre-operative ray treatments make laryngectomy more successful. For extensive cancer it is a very good treatment. Recently there have been improvements in technique and it has been found that the best results can be obtained only by very wide excisions, with removal of enlarged cervical lymph nodes in one block, preferably at the same operation. To be successful the sterno-mastoid muscles are usually removed. The internal jugular vein is tied on the affected side. Some surgeons now tie both veins. Even very extensive disease involving the pharynx, post-cricoid region, and nodes can now be treated successfully by laryngo-oesophago-pharyngectomy.

Laryngo-fissure

In 1900 Butlin and Semon published a paper showing that "thyrotomy" (as they called it) and local excision of early localized cancers of the vocal cord produced as many cures as laryngectomy, with far less mutilation. This

created a sensation and was vigorously contested. For many years it was unpopular in all other countries except England, but before long StClair Thomson, Chevalier Jackson, and the Mayo Clinic published a large series of cases with 75% of five-year survivals. It was always a good operation and still is the best surgical treatment for early lesions. It is a treatment which can be perfectly well carried out in any general hospital by an experienced surgeon. The mortality should be negligible. Nearly all patients have a useful voice afterwards, enabling them to carry on their occupations. A word of caution is necessary. Laryngo-fissure must be undertaken only for the removal of superficial growths which are absolutely localized to the anterior part of the cords. Even a growth which extends into the anterior commissure and affects only a small part of the opposite cord can be successfully removed, but any wide excision of both vocal cords is apt to cause stenosis and the voice may be seriously damaged. As has already been explained, it is sometimes difficult to be certain that the growth is entirely intrinsic, particularly if it is ulcerated and causing loss of movement of the cord. If the cord is completely immobile the disease is probably too advanced for local excision. Undoubtedly, early lesions can now be safely treated by laryngo-fissure.

Radiotherapy : 1. High-voltage X Rays

In 1898 Lewis Jones, using small tubes, began treating cancer with small doses for long periods, up to six months, at St. Bartholomew's Hospital. Since then an enormous amount of money has been invested in equipment which has been improved almost yearly. A colossal amount of research has been done by scientists, and accurate doses can now be given even to deep-seated lesions. More patients have been treated by x rays than by any other method. The medical profession and their patients have been told that it is safer than surgery and gives equally good results. As more powerful tubes have become available with an output of millions of volts, and of course costing more and more, the public have been assured that even better results will be obtained.

Unfortunately x-ray therapy has been disappointing. Cures are still reported only by special cancer clinics using the latest high potency equipments and by very experienced specialists. Radiotherapists should not treat cancer of the larynx with inferior equipment. They have no hope of good results.

To justify such an assertion it is necessary to analyse the evidence to support it. This can easily be obtained from the general hospitals. There can be little doubt that their x-ray treatments for cancer of the larynx have been a failure. It is extremely doubtful whether this bad habit will be cured for a long time : it has obtained such a hold on the public, in spite of its being a long harsh treatment lasting from six to eight weeks. The patient's health often suffers, severe reactions are common, hoarseness and pain persist, the tissues remain swollen, and it may be very difficult to decide whether the growth has been arrested. These signs may be due to perichondritis. Lastly, the skin and deep tissues may be damaged. After a time a new doctor may be consulted and the patient is told that he requires "a few more rays." Repeated ray treatments are often disastrous, and should rarely be given except for palliation of symptoms after recurrence. The following is a typical history :

A patient who complained of persistent hoarseness, probably due to perichondritis, was sent to the country to recuperate. The symptoms worried him, and he consulted a local radiotherapist, who, without a biopsy, advised "a few more x rays." A full course was started, but soon caused such inflammation that a tracheotomy became necessary. He suffered agonizing pain and died in six months.

It is only fairly recently that accurate localization of x rays has been possible. After a full course there may be severe reaction, and if the skin has been damaged healing may be affected.

A patient who had a recurrence two years after needling was treated with high-voltage x-rays and teleradium. Although the skin was scarred laryngectomy was risked. The flaps sloughed and when the wound had recovered a plastic repair with a large pedicle flap was performed, but this also failed to heal. Two further operations were necessary to close the fistula, but he died shortly afterwards of cancer.

Extrinsic cancer is hardly ever cured by x rays alone, and never if the lymph nodes are diseased. But the treatment is of the greatest value for the relief of symptoms and for arresting the disease. Occasionally, dramatic results are obtained, and it is difficult to explain why this happens so rarely.

A woman aged 80 had an extensive carcinoma, which obstructed her larynx and required tracheotomy. A full course of deep x rays was given by Finzi, and although the lesion did not shrink much it became inactive for four years, when she died of old age. Another cauliflower lesion almost filling the larynx in a man aged 79 entirely disappeared after x-ray therapy until his death. A still more remarkable cure should be mentioned. A man of 33 was treated by laryngo-fissure and remained perfectly well for 23 years. He then had a recurrence, and in a short time the growth fungated through the scar and tracheotomy became necessary. After x-ray therapy by Finzi in 1932 it disappeared and the patient is still living 20 years later, though a tracheotomy tube is necessary on account of stenosis.

2. Pre-operative Radiotherapy

It is known that even small doses of x rays check mitosis temporarily and often shrink new growths to a large extent. In 1925 it was decided to give this treatment a trial: small doses totalling 1,000 to 1,500 r were given on three to five days and needles were inserted a day or two later. In all, 26 patients were treated as shown in Table III.

TABLE III

	Stage I (6 Cases)	Stage II (17 Cases)	Stage III (3 Cases)	Survival All Stages
3-year survivals ..	5	9	1	58%
5- " " " ..	5	7	0	46%

3. Teleradium

This seems to be a better treatment than high-voltage therapy for many deep-seated cancers in different parts of the body. For instance it is undoubtedly the best treatment for new growths in the tonsil and post-nasal space. This is fortunate, because surgery is useless. In the larynx it appears to be more successful than x rays. It is less harsh, the reactions are milder, and the results are as good as any other treatment. Stanford Cade, to whom I am greatly indebted for advice for so long, has now abandoned other ray treatments, including radium needling, and uses the "bomb" for all stage I early lesions and for some intrinsic stage II growths. The Royal Cancer Hospital (London) has the largest series of laryngeal cancers in England. Lederman uses teleradium exclusively, and laryngectomy only for "failed bomb" cases.

To summarize, the drawback to both x rays and teleradium is largely the cost. They require a house to live in, an apparatus which is more expensive each year, and which requires constant repairs—not to mention replacements—and a large and highly trained staff of specialists to run the ship. Obviously it will be impracticable for use in general hospitals, and it is unlikely that there can be more than a few of these units carefully placed in special cancer clinics throughout the country.

The Finzi-Harmer Operation

In 1924 Ledoux, of Brussels, described his "fenestration" operation, which consisted in removal of the cartilage from one side of the larynx and the insertion of short radium needles into the growth. After a visit to Brussels, where we saw some of his patients, it was decided to try the treatment. But to prevent disturbing the growth and risking

infection of the wound the needles were placed longitudinally outside the perichondrium covering the lesion. Our second patient, who had an extensive carcinoma and could only whisper owing to fixation of the vocal cord, had been advised to have his larynx removed, but when told that he could be treated by radium first he agreed to take the risk. He was cured by needling and remained well with a strong voice for six years, when he died, of all things, from psittacosis.

If the lesion is not causing severe obstruction to breathing and one vocal cord is moving, intratracheal anaesthesia is safe and preferable to local injections, but, to prevent troublesome bleeding, infiltration of the whole region with procaine and adrenaline is also advisable. The growth itself should not be infiltrated. Two incisions, $2\frac{1}{2}$ in. (6.3 cm.) long, are made, one transversely above the thyroid cartilage with two-thirds of it on the affected side; the other vertically, over the side of the larynx to the upper rings of the trachea. Two skin flaps are turned laterally to expose the side of the larynx and the infrahyoid muscles. The latter are split from the hyoid bone to the trachea. Bleeding is arrested with coagulating diathermy or ligatures. A mastoid retractor is introduced to separate the muscles and to expose the lateral ala of the thyroid cartilage. The perichondrium is divided with cross cuts and reflected. The lateral ring of the cricoid cartilage is also exposed. With a small curved elevator the perichondrium under the lower margin of the thyroid is separated and a small piece of it is isolated and removed with cutting forceps. This is continued until nothing remains except a narrow frame along the upper and posterior borders. In front, the window should be carried almost to the middle line, leaving the centre keel intact. The upper edge of the cricoid ring is also stripped and notched so that the needles can be pushed under it (Fig. 5). The tissue beneath it is very thin and the dissection must be done with care. On no account must the growth or the larynx be punctured. As already stated, in advanced cases the growth may invade the perichondrium or even the cartilage. This is a serious complication, and unless the lesion is completely encapsulated it can seldom be cured by needling alone. Very rarely there may be upward extension of the growth to the base of the epiglottis, necessitating removal of the greater cornu of the hyoid bone (Fig. 6).

The wound must be quite dry before the needles are inserted: each has two silk threads, and each one must be securely fixed with catgut sutures top and bottom.

Unfortunately, for six years it was not realized that the needles are apt to slip out of place and to bunch together: this happened to a distinguished physician who had an extensive bilateral growth for which seven specialists had

FIG. 5.—The fenestration operation.

FIG. 6.—The extended fenestration operation.

advised laryngectomy as the only safe treatment (Fig. 7). He had just heard of radium, and, although at that time only 16 patients had been treated with it, he decided to try it first. A bilateral fenestration was performed. Afterwards he had such violent vomiting that an x-ray film was ordered, and this showed that all the needles had slipped and were

FIG. 7

lying in a bunch by the side of his trachea. The needles were replaced the next day. In three months he resumed full work and was able to lecture with a good voice. He made a daring decision, and is still well

after 24 happy years. Because of the possibility of the needles becoming displaced every patient must have a skiagram taken 24 hours after operation.

Bilateral Fenestration.—Lesions of both vocal cords are difficult to cure, and unless the patient is well and has a resonant voice in two or three months laryngectomy should be performed. Fourteen patients had bilateral needling. One had fairly early lesions of the cords and was cured for ten years. He then had a recurrence, but died after laryngectomy. Eleven had extensive lesions which could have been treated only with laryngectomies. Seven died in the first two years. One died of old age in five years. Three are living, for 8, 19, and 24 years, the last the physician mentioned above.

Before closing the wound the cavity should be powdered thickly with sulphanilamide or soaked with 1:1,000 acriflavine solution. The threads are then tied together securely and cut short near the bases of the needles, but leaving one long thread which is fixed to the skin and acts as a guide when they are removed. The infrahyoid muscles are sutured together with catgut over the needles to keep them close to the growth. The transverse skin incision is closed accurately with fine interrupted sutures, which are removed when the wound has healed. In the lower incision, double threads of different colours are inserted, one group cut short to close the wound until the needles are removed, the others kept long for tying afterwards. No drainage is necessary.

Tracheotomy.—From 1924 to 1936 it was difficult to gauge the dose, and later researches showed that this probably varied from 3,000 to 13,000 r in different patients. It is not surprising, therefore, that many of them had severe reactions, with redness, filming, and oedema—particularly of the arytenoid cartilages. For fear of dyspnoea eleven tracheotomies were performed, the tubes being retained until the reaction subsided. Tracheotomy caused serious complications. All the wounds became infected and discharged pus for several weeks. The inflammation sometimes caused necrosis of the cartilages, and healing was naturally very slow. Five other patients required tracheotomy for recurrence. Since 1936 no tracheotomies have been performed after needling. It was found that if a growth was large enough to cause serious obstruction to breathing fenestration was not advisable unless one vocal cord was freely movable. Temporary dyspnoea after the operation can be relieved by retaining the intratracheal tube if necessary for a day or two. If, however, the difficulty of breathing is severe the trachea can be exposed, but not opened unless it is absolutely necessary: only two of the patients required this.

Removal of Needles.—If the wound is not inflamed and there is no swelling in the larynx the needles are usually retained for a week. For removal gas and oxygen or thiopentone can safely be given. The lower wound is opened and the needles are easily removed. Usually there is a small amount of blood-stained serum. The wound should be

washed out with acriflavine, 1:1,000, and sutured completely. "Mastisol" is painted on the skin, which is covered with a thin layer of gauze.

Wounds which become seriously infected may be very troublesome. Haemorrhage, sometimes severe, may occur. Extensive sloughing of the tissues may be caused. It is in this type of wound that perichondritis supervenes. Later on it may be followed by necrosis. The treatment of infected wounds is important. All stitches should be removed. The wound should be widely opened, if necessary under an anaesthetic. Debris and sloughs should be removed. The wound should then be packed with gauze soaked in penicillin and sulphanilamide. If the dressing is repeated frequently serious infection is usually controlled in a few days unless there is a communication with the interior of the larynx at the time of the operation which caused the infection. Such wounds may take weeks to heal.

The Dose

A colleague lecturing to students about certain cancers said, "Use radium—plenty of it." This delightful aphorism does not apply to the larynx, which is a difficult customer to please. Great care must be taken not to overdose the patient. From the physical standpoint the great advantage of the radium implant is that irradiation is highly localized, so that there is the minimum interference with unaffected tissues. On the other hand, it is virtually impossible to give a uniform dose to the whole vocal fold by this method. It is true generally, however, that when an irradiated volume is fairly small some non-uniformity in the dose distribution is tolerable provided that the lesion itself receives an adequate dose.

In first treatments, from 1924 to 1936, eight 1-mg. needles were placed touching each other in the window, their ends being tucked under the upper margin of the thyroid above and the cricoid below. It was soon realized, however, that in the middle the dose was too high, causing severe reaction or even necrosis, while at the ends it was inadequate. It varied from 13,000 to 3,000 r. In an ideal arrangement the dose in a week should be about 6,000 r to the anterior half of the cord, but there is a marked fall posteriorly to 3,000 r and also below the free margin of the cord with such short needles of only 16 mm. active length. In spite of this some surprisingly good results were obtained, although these patients must have been overdosed.

Since 1933, when the practice of removing part of the cricoid cartilage was adopted, longer needles have been used though the total amount of radium was approximately as before. As a result, a more uniform distribution of dose is obtained, particularly below the vocal fold. It has been found beneficial to add a transverse 1-mg. needle at the lower ends of the vertical needles in those cases in which the level of the vocal fold is much below the mid-point of the fenestrated area—for example, in many females or in lesions with subglottic extensions.

FIG. 8.—Dosage.

Stage I: Early Intrinsic (37 patients).—Early lesions were confirmed by removal of the thyroid cartilage in every case. One patient died from the operation, three from cancer (one after 10 years), and sixteen from other causes. Seventeen are still living. Most of the survivors have strong resonant voices. The survival rates are shown in Table IV.

Stage II: Advanced Intrinsic (72 patients).—Usually these were unilateral, extensive, and apparently intrinsic with no enlarged lymph nodes. Twelve were bilateral. Soft tumours, if movable, responded better than the hard nodular ulcerated types. There were five operative deaths from chest infections, which were common when tracheotomies were performed, all of them before the introduction of antibiotics. Forty-two died of cancer, 31 in less than three years, six during the third year, but only five after this critical period. Among these 72 patients 26 survived with their larynges and excellent voices for periods ranging from five to twenty-four years. The survival rates are shown in Table IV.

Stage III: Extrinsic (9 patients).—These patients, who were found to have definite extrinsic lesions without obvious enlargement of cervical nodes, were needled and all of them died within three years. Needling alone has therefore been a failure. But, excepting for two who died of heart failure after operation, seven were temporarily improved for two to three years. Here again, laryngectomies should have been performed while the disease was arrested, and I regret that this was not done.

Summary

Lesions suitable for radium needling are therefore the following:

(1) Early lesions (stage I). Even if the vocal cord is fixed. Lymph nodes are never affected in this group.

(2) Localized lesions in the anterior commissure without involvement of the base of the epiglottis or of the tongue. In this region the dose is always a high one and needling usually succeeds in controlling the disease.

(3) Extensive lesions that appear to be intrinsic (stage II).

(4) Subglottic lesions (really stage III). In a few patients good results have been obtained and there is no risk in trying this treatment first, but laryngectomy should be performed early, in a month or two, if the swelling persists.

(5) Lesions of the false cord and vestibule (stage III). These growths are unusually malignant and difficult to cure. Probably needling plus laryngectomy is the best treatment.

ENVOY

In putting on record the results of 30 years' work with this particular treatment for intrinsic carcinoma of the larynx it would seem to be reasonable to claim that the method has been unduly neglected. I am aware that as good figures have been published claiming that telerradium is superior to interstitial needling for early lesions. I have always maintained that cancer should be treated in special centres by the united efforts of a team of specialists in this disease. Yet there is still a place for simplicity in surgery, and no one can deny that the establishment and maintenance of a telerradium unit is extremely costly. Radiation techniques become increasingly complex and require more and more planning and space and time. The method which we have adopted (and which has been described, possibly a little grudgingly, as "a piece of brilliant empiricism") is relatively cheap and extremely simple in the hands of a competent surgeon. It gives really excellent results if used for the right patient. And it is here, of course, that the clinical experience gained in a long apprenticeship in laryngology counts.

The proof of the pudding is in the eating. I think that this has been a good pudding and that it would be a pity if the recipe were lost.

FOLIC-ACID-EXCRETION STUDIES IN THE INVESTIGATION OF MALIGNANT DISEASE

BY

RONALD H. GIRDWOOD, Ph.D., M.B., Ch.B.
F.R.C.P.Ed., M.R.C.P.

Senior Lecturer in Medicine, University of Edinburgh

When a test dose of 5 mg. of folic acid is injected in a normal individual a significant proportion is promptly excreted in the urine. Most of this excretion occurs within a few hours, but for metabolic studies it is advisable to collect the urine for twenty-four hours after the injection. It has been shown that the urinary excretion of folic acid is diminished in many cases of pernicious anaemia (Bethell *et al.*, 1947; Girdwood, 1951, 1953). In a short review of the subject (Girdwood, 1952a) it was suggested that the controls used in the studies of pernicious anaemia patients were unsatisfactory, and that patients with other forms of anaemia should be employed. Accordingly the present investigation was started as a study of folic acid excretion in various types of anaemia. At an early stage it was found (Girdwood, 1952b) that, of eight patients with iron deficiency anaemia, folic-acid excretion was diminished in four. All of these four suffered from carcinoma. It was decided, therefore, to investigate further the urinary folic-acid excretion in patients suffering from malignant disease and from various non-neoplastic conditions. About this time it was reported (Swendseid *et al.*, 1952) that folic-acid excretion was impaired in leukaemia. The patients in the present investigation were all given 5 mg. of folic acid subcutaneously.

Methods and Materials

The estimation of the urinary content of folic acid was carried out microbiologically. Under the conditions of the test the growth of *Streptococcus faecalis* in a suitable medium depends upon the amount of folic acid present in that medium. The growth of the test organism in tubes containing that medium and various dilutions of urine is compared with that in tubes containing the medium and dilutions of a standard solution of folic acid.

Estimations of folic acid were by the method of Teply and Elvehjem (1945), *Str. faecalis* R being used as the test organism. Estimations of citrovorum factor were by a modification of the method of Sauberlich and Baumann (1948) with *Leuconostoc citrovorum* as the test organism. In both instances turbidity readings were carried out in a Spekker photo-electric absorptiometer after incubation at 37°C. for 16 hours. The resting urinary content of folic acid is so small that no correction requires to be made for it in the folic-acid readings. The proportion of folic acid excreted as citrovorum factor is very small, as shown in the accompanying Tables, and the "folic acid" figures include any growth activity due to citrovorum factor. The citrovorum-factor readings have not been corrected for the resting urinary content of citrovorum factor, which on the average is of the order of 1 µg.

The folic acid was given by subcutaneous injection from a tuberculin syringe, and was taken from one or other of two batches of "folvite" that had been tested by us and found to contain 15 mg. of folic acid per ml. Several batches were rejected as they contained more than the stated amount. The volume injected was 0.33 ml.

Twenty-four-hour urine collections were put in brown bottles containing toluene and a phosphate buffer of pH 6.8. The greatest possible care was taken to ensure that the urines were total 24-hour specimens. The specimens were kept in a refrigerator at 4°C., and readings were usually