formalinization is increased, the toxicity is reduced, but, unfortunately, so also is the immunizing efficiency. Veldee has studied the method extensively during the past few years. He inclines to the view that formalinization must not be carried too far; unless approximately 500 skin test doses of toxin per cubic centimetre are left, high immunity is not secured, even with three doses and with the addition of alum. Here again it must be pointed out that experience indicates that progress would be more rapid in England if opportunities for immunizing large comparable groups of children were available. R. A. Q. O'Meara and H. J. Parish kindly allow me to say that they have been working with toxin-antitoxin mixture and with floccules as immunizing agents, but the few results available do not yet warrant publication. G. A. H. Buttle has been endeavouring to immunize rabbits rapidly by several modifications of the ordinary methods and by the use of the toxin of unusually high value described by O'Meara, but has not yet obtained results that satisfy him.

Whooping-cough

The work of Madsen in Scandinavia and Sauer in U.S.A. offers considerable hope. Madsen states that of 1,800 people vaccinated 25 per cent. escaped infection, whereas only 2 per cent. of 450 non-vaccinated people escaped. Sauer found that of 380 young children who were vaccinated and suffered exposure not one became infected. An odd feature is that, while Madsen finds that children rapidly become immune, Sauer does not expect adequate immunity to develop for about four months. Jundell in Sweden vaccinates adult volunteers who have had an attack in the past, and hopes in this way to raise the titre of the antibody in the blood, thus obtaining an equivalent of the invaluable "convalescent measles serum" for protection of groups of young children in contact with sufferers from the disease.

General Note

Two thoughts may occur to the practitioner who is interested in this field of work. Reflecting on the resistance of the average parent to vaccination in any form, he will perhaps conclude that if the enthusiast gets his way there will be too much immunization. He must then remember that diphtheria alone causes 40,000 to 60,000 cases a year in England and 2,000 to 3,000 deaths, and that if we adopt Dr. Glover's estimate of the loss of time due to infectious disease in large schools the lost educational time must cost the community a huge sum each year.

The second thought will probably be one of some regret that progress is so slow. The lag is almost wholly on the human side. The immunologist, in England at all events, is always far ahead of the clinical investigator; with greater opportunity of using, under proper safeguards, different antigens on large groups of children, we should progress faster.

G. Serdaris (*Thèse de Paris*, 1934, No. 64) describes the antimalarial campaign carried out in a period of six months in a small area (Rhododaphnia), of the Peloponnese under the auspices of the International Health Division of the Rockefeller Foundation and the School of Hygiene of the Athens Ministry of Health. Although a definite opinion cannot be expressed until the end of three years, the results hitherto obtained have been very good. The number of *A. maculipennis* and *A. superpictus* has considerably diminished, and the splenic index has decreased, while the haematological index has increased. Quinine salts only were used for treatment.

IRRADIATION TREATMENT OF MALIGNANT INTRATHORACIC TUMOURS

BY

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In September, 1927, one of us (F. G. C.), with Dr. Carlyle Potter, published a follow-up of cases of malignant intrathoracic tumour treated by x rays.¹ The results were most discouraging, for out of fifty-nine cases one alone survived. The result in this case, however, was so remarkable that it was impossible to do otherwise than encourage further trial and further development of the treatment. The patient, a young woman aged 25, was under the care of Lord Horder in St. Bartholomew's Hospital in 1923. She was desperately ill with a large mass in the mediastinum, many large glands in the neck, and bilateral pleural effusion. Microscopical examination of a cervical gland showed lymphosarcoma. She still survives in excellent health, and the skiagram is absolutely normal.

The authors of the article were unable to report any prolongation of life, apart from this one instance, and only temporary or no appreciable alleviation of symptoms. In the last few years, however, the results from treatment have seemed to the present authors to be better. Many impressive cases of relief of symptoms have been noted, and also the complete disappearance of the mass in the chest in several instances. It seemed desirable, therefore, to make another investigation into the results of treatment in a series of more recent cases.

Diagnostic Criteria

The first criterion is the proof positive—namely, microscopical examination of a section of the thoracic growth or of a metastasis. This must be accepted as the most convincing evidence, in spite of occasional difficulties of interpretation. The material for examination has been obtained by thoracotomy in seven cases, by bronchoscopy in seven cases (this excludes cases subsequently confirmed by post-mortem examination, otherwise the number would be larger), by removal of a metastasis in five cases, and from post-mortem material in nineteen cases.

The second criterion is clinical evidence: symptoms, signs, course of the disease, and exclusion of other conditions by special investigations. The third is radiological evidence.

It would occupy much space if we attempted to elaborate the last two criteria, nor is it perhaps quite within the scope of this paper. We can say, however, that no doubtful case has been included, and we are confident that the rigid criteria adopted would be accepted by all workers as adequate proof. The few difficult or doubtful cases are described in some detail later.

Our material consists of seventy cases from St. Bartholomew's Hospital, the Royal Chest Hospital, Victoria Park Chest Hospital, and private practice, from 1927 to 1933.

We are indebted to the following physicians and surgeons:

Dr. Geoffrey Bourne, Professor Langdon Brown, Drs. J. B. Christopherson, E. H. Colbeck, E. R. Cullinan, Geoffrey Evans, H. Morley Fletcher, Professor Fraser, Drs. E. A. Gow, G. Graham, Sir Percival Horton-Smith Hartley, Dr. R. Hilton, Lord Horder, Drs. C. M. Hinds Howell, D. Barty King, A. J. Scott Pinchin, Arnold W. Stott, H. E. Symes Thompson, F. E. S. Willis, W. B. Wood.

Sir Thomas Dunhill, Professor Gask, Sir Charles Gordon-Watson, Mr. L. B. Rawling, Mr. J. E. H. Roberts, Mr. H. G. B. Russell, Mr. R. M. Vick.

The cases presented are as follows:

	Cases
1. Bronchial carcinoma treated by x rays ...	44
2. Bronchial carcinoma treated by radium or radium emanation	12
3. Malignant tumours other than bronchial carcinoma treated by x rays:	
(a) Primary in the chest	2
(b) Secondary carcinoma	5
(c) Secondary sarcoma... ..	2
4. Tumours of doubtful nature	5

In each of the cases treated by x rays at least ten applications were given. In a great number of other cases treatment was abandoned in the early stages of the course, and these have been excluded from this series.

Treatment by Irradiation

It must always be assumed in dealing with neoplasm of the lung that the glands of the mediastinum are involved or are likely to be involved, and must therefore be thoroughly treated. Lymphosarcoma requires a much smaller dosage than carcinoma and endothelioma. Occasionally the early treatments can only be applied from one or two directions owing to the patient being too ill to be moved. Later in the treatment, as the patient improves, other ports of entry can be used. The treatment is spread over two, three, four, or five weeks, and is given on five or six days each week.

Principles of Treatment

1. To give a sufficient dose to the whole growth and to the lymphatic glands likely to be affected.
2. Without restricting the dose on the growth, to give as small a volume dose to the general tissues of the patient as is consistent with efficient dosage to the tumour and lymphatic glands.
3. To damage the lung as little as possible. Lung which has been the site of old inflammation, tuberculous or otherwise, is very radio-sensitive, and exacerbation may result.
4. To cause no damage to the skin beyond a severe erythema, which ultimately clears up. With lymphosarcoma only a mild erythema will be necessary, but with carcinoma a severe erythema verging on blistering is usually required.
5. Some workers, including one of us (N. S. F.), consider lipiodol undesirable in a lung which is to be subjected to irradiation, on the ground that residual lipiodol gives out secondary radiations of long wave-length, which cause damage and necessitate curtailment of the requisite course of treatment.

Technique of Treatment

Various techniques have been used in our cases. As a rule a number of ports of entry are employed, but occasionally, with a very radio-sensitive tumour, only anterior and posterior fields are necessary. Various different plans have been used according to the situation of the growth: if in the anterior part of the mediastinum, a number of relatively small ports of entry are used converging on the

mediastinum; but, if the growth extends far into the lung, larger fields are usually employed—generally four—at an angle of 45 degrees to the direct anterior and direct posterior, taking in both the lung growth and the mediastinum, and decentred towards the side of the growth. In other cases, where the growth is almost entirely on one side and far into the lung, a direct anterior and posterior field is used, slightly to one side of the middle line, and this is supplemented by a lateral field on the affected side.

In most cases the filtration has been about 0.5 mm. of copper and 1 mm. of aluminium, and 180 kV continuous current on the tube, but in our later cases a Thoraeus filter has been used, which is equivalent to about 2.7 mm. of copper, with 200 kV continuous current, and at the present time we are using for our private cases an even higher voltage, up to 300 kV Villard circuit current with a filter of 0.6 mm. tin + 0.25 mm. copper + 1 mm. aluminium, equivalent, with the wall of the tube, to about 4 mm. or more of copper. With the increase in filtration the number of roentgens (r) to produce an erythema dose increases considerably, and the number of roentgens necessary on the growth also increases.

For a lymphosarcoma or a very radio-sensitive tumour it is necessary to give about 150 to 180 per cent. of an erythema dose, spread over a fortnight; a larger dosage must be given if it has to be spread over a longer period, owing to the patient not being able to tolerate the ordinary dose at first.

With a carcinoma of the lung or resistant growth, about 250 to 300 per cent. is given, spread over a month or six weeks.

The erythema dose we reckon with 0.5 mm. copper and 180 kV is 650 roentgens: the erythema dose with a filter equivalent to about 0.4 mm. of copper and 300 kV is approximately 1,000 roentgens.

Effects of Treatment

It is always difficult to reach a definite conclusion as to the results of any particular line of treatment, and care must be taken in assessing the results. This difficulty applies particularly in the case of bronchial carcinoma, because the criteria of improvement are difficult to define on account of the well-known spontaneous variation of symptoms. In the first place there may be obvious clinical relief of urgent pressure symptoms; secondly, the effect of treatment on the size of the tumour may be observed in serial skiagrams; and lastly, the result as regards the duration of life may be considered.

The first of these criteria is a matter of clinical observation. In calculating the size of the tumour on the x -ray film only very gross changes should be admitted, for the direction and penetration of the rays may cause minor apparent changes which are of no great significance. We therefore propose, in judging the effects of treatment on the size of the tumour, only to include cases in which the shadow has practically disappeared. Finally, the duration of life from the date of the beginning of treatment may be considered; the advantage of this is that it provides a fixed point from which calculation may be started, and it is thus more definite than calculations which are based on the total duration of symptoms, in which case no very definite point of commencement can usually be fixed.

The forty-four cases of bronchial carcinoma treated by x rays can be divided into the following groups:

1. *Cases which Showed Great Improvement.*—Twenty-three cases are included in this group, primarily on the ground of symptomatic benefit. In ten of these relief of pressure symptoms was rapid and the result dramatic. In eleven there was gradual improvement over a period

of weeks. In the remaining two cases the shadow in the x -ray film disappeared, but it is noteworthy that there was little or no improvement in the condition of the patient. Serial skiagrams showed almost complete disappearance of the shadow cast by the primary growth in nine cases, and complete re-expansion of a collapsed lung in two cases. The ultimate fate of the cases is as follows: five are known to be alive at the time of writing, thirty-two, thirty-one, twenty-four, six, and five months respectively after the commencement of treatment. In the first three of these cases it is probable that life has been greatly prolonged in addition to the symptoms being relieved; in one of these the diagnosis has been confirmed histologically. The remaining eighteen patients are all known to have died, and the average duration of life after beginning treatment was 9.7 months. Only three patients survived more than fifteen months, dying respectively in thirty-six, seventeen, and sixteen months.

2. *Cases which Showed Slight Improvement.*—In seven cases there was incomplete but definite relief of symptoms, and in this group the average duration of life was 8.6 months. The fact that the average duration of life in these two groups is about the same would appear to suggest that great symptomatic improvement or disappearance of the shadow in the skiagram does not necessarily indicate prolongation of life.

3. *Cases which did not Respond to Treatment.*—In fourteen cases there was no change in the condition of the patient after a course of treatment. In two, the date of death could not be ascertained; the average duration of life in the remainder was 5.4 months.

It does not seem that x -ray treatment has any great effect in prolonging life in this disease, except possibly in rare cases; it is quite definite, however, that this treatment can relieve the more urgent and distressing symptoms in about two-thirds of the cases, and can cause local disappearance of the tumour. In our opinion there is sufficient evidence of symptomatic improvement to justify the adoption of this line of treatment in all cases in which obstructive or irritative symptoms are present. The changes in the size of the tumour, as demonstrated, are sufficient to justify the hope that improvement in the technique of treatment will in the future yield greatly improved results.

4. *Cases Treated by Radium.*—In ten cases in which radium or radon was introduced directly into the growth through a bronchoscope the average duration of life after the operation was 2.4 months. In no case was any dramatic improvement recorded, and, in two, death resulted from haemorrhage shortly after the operation had been carried out. The results in this series are therefore definitely discouraging. In two further cases radium was inserted into the tumour through the chest wall. In one of these marked temporary diminution of the tumour occurred; in the other there was decided improvement in the general condition of the patient for a few months; death occurred eight months after the operation.

Other Intrathoracic Tumours.—Nine cases of malignant tumour other than bronchial carcinoma are included in this series. This group is composed as follows:

Secondary hypernephroma	...	...	2 cases
Primary sarcoma	...	...	1 case
Secondary sarcoma ? appendix	...	...	1 "
Secondary sarcoma ? bladder	...	...	1 "
Secondary carcinoma breast...	...	...	1 "
Secondary sarcoma fibula	...	...	1 "
Secondary carcinoma thyroid	...	...	1 "
Endothelioma ? from thymus	...	...	1 "

In four cases the treatment did not appear to have any effect. In two cases, secondary to hypernephroma and to carcinoma of the bladder, haemoptysis appeared to be controlled by irradiation; the intrathoracic deposits in the case of sarcoma of the fibula diminished greatly in

size under the treatment, and the cough was much relieved.

The remaining two cases are remarkable in that the patients are alive eleven and twenty-one years respectively after treatment.

The first was a patient under the care of Sir Thomas Dunhill and Dr. Thursfield. A mediastinal tumour was present, causing breathlessness, swelling of the neck, distended veins over the back and chest, shoulders, and arms, and a gland or prolongation of the tumour in the right supraclavicular region. A sternal flap was made and the tumour exposed. This was thought to be an infiltrating sarcoma, and nothing more was done. Microscopical examination of the portion removed revealed an endothelioma of apparent thymic origin. Courses of x -ray treatment were commenced in August, 1923. The tumour entirely disappeared, and the patient is alive and well at the present time.

The second was also a patient under the care of Sir Thomas Dunhill. She was first seen in November, 1913, when a nodular goitre on the right side was removed. Section suggested malignancy. In 1918 a small nodule was removed from the extreme right edge of the scar. Section showed an almost solid mass of epithelial cells, resembling thyroid cells. The patient remained well until 1927, when a haemoptysis occurred (half a cupful). The skiagram at this date showed rounded nodules in both lung fields. These increased rapidly, until there were many nodules of a perfectly rounded shape in both lungs. X -ray treatment was therefore commenced in March, 1928. The haemoptysis ceased and the patient remained in good health, and has done so until the present day, although the nodules have grown in size and number.

Finally, there are five cases to be considered in which both the clinical picture and the x -ray appearance suggested malignant tumour, in which either cure or great relief has occurred. Unfortunately, in none of these cases have we histological proof of the nature of the mass. They are of such interest that they are worth describing in detail.

The first was a case included in the original follow-up in 1926. The patient, E. M., was under the care of Dr. Robert Hutchison at the London Hospital in 1924, with swelling of face and neck, and a shadow in the skiagram suggestive of growth in the right upper lobe. The diagnosis was malignant growth. X -ray treatment was given, and the patient made a complete recovery. He was seen by one of us (F. G. C.) in 1926, when it was thought that the original diagnosis was probably mistaken, and that it was a case of dense fibrosis and not malignant disease. It fortunately happened, however, that we were able to keep in touch with the after-history of the case. He died in 1933 of intestinal obstruction, when a columnar-celled carcinoma of the descending colon was found post mortem, and, through the kindness of Dr. W. Smith, we were able to obtain the result of the examination. There was marked dilatation of the azygos vein, there were universal pleural adhesions on the right side, and a firm mass was present at the hilum of the right lung, about two by one and a half inches in size. Some fibrosis was present in the lung itself. Section of the mass showed merely much fibrosis with round-celled reaction. The pressure symptoms originally suggested malignant growth of the lung. We can make no further comment.

The second patient,* a woman aged 34, was under the care of Lord Horder and one of us (N. S. F.) in 1930. The skiagram showed an enormous mediastinal mass, extending into and occupying most of the left lung field. This was treated by x rays, and the entire mass disappeared, and the patient is alive and well to this day. There must remain a doubt whether this was a primary mediastinal lymphadenoma or a lymphosarcoma.

Case number three was a man aged 57, seen by one of us in 1930, at the City of London Chest Hospital, Victoria Park. The patient complained of cough, shortness of breath, loss of weight, and haemoptysis. There was clubbing of the

* There has been a recurrence in this case in May, 1934. She has again been treated by x rays and the shadow has again disappeared, and there is now no evidence of disease.—N. S. F.

fingers. The skiagram showed a dense mass filling the whole of the right upper lobe. Exploratory thoracotomy was performed by Mr. Romanis, when a large inoperable "growth" was encountered. Unfortunately no piece was taken for section. It was assumed to be a carcinoma, and the operation was abandoned. He was then transferred to St. Bartholomew's Hospital, where he was given twenty applications of x rays. The mass almost entirely disappeared, leaving considerable fibrosis. The patient is still alive and well, but the nature of the mass remains in doubt.

The fourth case was that of a lady aged 55, seen privately (F. G. C.) first in July, 1932. There was pain in the back and shortness of breath and loss of weight. She had been fairly well until a year previously, when the symptoms commenced. When first seen the patient was extremely ill, with dyspnoea, stridor, and slight clubbing of the fingers. There was intense dullness over most of the left side, almost down to the base, where she was resonant, and where breath sounds were present. Over the dull area breath sounds were absent and vocal resonance diminished. There was a loud surging murmur to be heard in the second intercostal space. She was explored deeply on two or three occasions, when pure blood was obtained with great ease, the syringe rapidly filling. The heart was displaced away from the mass. She was so ill that an exploratory thoracotomy was considered to be unjustified by Mr. J. E. H. Roberts. The diagnosis was a large innocent tumour or a lymphosarcoma: Wassermann reaction negative. On going further into the history it was found that three years previously she had had severe pain in the left chest, which made her faint.

A full course of deep x -ray therapy was given, after which she made a most striking improvement, although the shadow remained unchanged. This improvement continued to December, 1933. The patient was able to take long walks and drive a car, and felt comfortable and almost free from symptoms. In December, however, she began to have choking attacks, and a further course of x -ray treatment was given. She was very ill both during and after this course, but is improving again, and able to lead an active life. The improvement in symptoms was most striking and dramatic, but again there was no change in the shadow. The nature of the tumour remains in doubt.

The fifth patient was a man aged 54, seen at Victoria Park Chest Hospital; he complained of pain in the right chest and axilla, much dyspnoea, loss of weight, and some cough. There was a large homogeneous shadow in the skiagram, occupying the middle zone of the right chest, and extending from the periphery inwards, almost touching, but not apparently involving, the hilum of the lung. The shadow looked like a localized pleural effusion. Several exploratory punctures were made, however, and no fluid was found. The Wassermann reaction was negative. It was regarded, therefore, as a malignant tumour, and twenty applications of deep x rays were given, from February to April, 1933. The tumour practically disappeared, and the patient is still alive and in reasonably good health. Within the last few weeks he has developed headache with papilloedema, almost certainly due to an intracranial metastasis.

Conclusion

There can be little doubt that since the publication mentioned at the beginning of this paper the results of x -ray treatment have improved very greatly. We have been able to quote many cases of great relief or complete disappearance of symptoms, and some where the undoubted malignant mass in the chest has entirely disappeared. While we cannot yet claim to have arrived at a cure, we have been able to quote two, and possibly three, cases in which this has apparently been obtained. In two instances, where the diagnosis has been proved beyond all manner of doubt, there has been a complete and lasting cure, but neither of these tumours was of bronchial origin.

In view of these conclusions we shall often be exercised, in making the decision, whether to advise this treatment to an individual patient or not. Relief from pressure symptoms can be expected in a certain proportion of cases, and if these are severe and distressing we can hardly

deny the treatment if it is available. In other cases, in view of the unavoidable expense of the treatment or the inconvenience caused by moving the patient to an institution, and the impossibility of guaranteeing a result and the severe reaction that may be suffered during or shortly after the cessation of the treatment, we may find it very difficult to make up our minds. A decision may have to be left to the patient or to the relatives. This attitude will not hinder the progress and development of the treatment of carcinoma or other malignant tumours of the lung by radiation therapy, because there will always be a large number of patients who will demand active measures, and who, particularly in the early stages, will demand this or some other form of active treatment.

In conclusion, we must not forget the dramatic improvement in the individual case in surveying the final result of the treatment critically and dispassionately.

REFERENCE

¹ *Lancet*, 1927, ii, 596.

SPECIAL CLINICS FOR DIABETICS (ORGANIZATION AND EXPERIENCES)

BY

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The organization required for prolonged treatment of diabetics has become of special interest, since, through the discovery of insulin, even severe cases of diabetes may be kept in a good condition permanently. Yet in actual practice, although the average duration of life among diabetics has increased (Joslin¹), periodic examinations have often demonstrated the results to be disappointing. According to Loewenberg and Noah,² one year and a half after discharge from the hospital only 10 per cent. of the patients were without glycosuria, and a large number showed increased fasting blood sugar or even acidosis. On extending his investigations over a period of six years, Reinwein³ stated that about 40 per cent. of the patients had died; of the remainder, 42 per cent. did not carry out the insulin treatment properly, and 28 per cent. admitted that they had not strictly adhered to the diet which had been prescribed for them. As a consequence, the largest Berlin panel organization (Allgemeine Ortskranken-kasse) found that the incapacity present among diabetics in most age groups was on the average twice as great as was the case among patients suffering from other diseases (Pryll⁴).

Some Causes of Unsuccessful Treatment

There are different reasons for the fact that the ultimate results in ambulatory practice are so unsatisfactory as compared with the success obtained through hospital treatment. The patients may find a certain diet which, although suitable while at rest in hospital, is insufficient while they are at work. By taking inadequate food they lower their tolerance, and the condition becomes worse, though very often exercises have a favourable influence on carbohydrate metabolism.

This has been proved by experimental as well as by clinical observations. After partial extirpation of the pancreas in the dog physical work diminishes glycosuria, but has no influence on it when the gland has been removed completely (Seo,⁵ Allen⁶). Correspondingly, clinical workers have found that in suitable cases exercises could improve the carbohydrate tolerance of diabetics (Trousseau,⁷ v. Noorden,⁸ Buerger,⁹ Allen, Stillmann, and Fitz,¹⁰ Hetzl,¹¹ Lawrence,¹² Joslin¹³).