Radioisotopes for the treatment of cancer

by C.B.G. Taylor*

The medical usefulness of X-radiation was realized soon after it was discovered in 1895, long before its physical origins were understood. A few years later the Curies were studying the even more penetrating rays from radium. Photographic medical radiology was the first development. Soon the effects of the new radiations on living tissue were being studied.

The effects were essentially destructive. A large dose of radiation caused reddening of the skin, damage to tissues, radiation necrosis, sterility. Small animals could be killed.

Such damage to growing matter suggested that cancer might be treated by the new radiation. Little was known about the cause or mechanism of cancer, but its manifestation as an uncontrollable "growth" was easy to see, and surgeons treated cancer by cutting away the diseased part. Could radiation replace surgery? Experiment showed that apparently it could. Not only did radiation inhibit the growth of these malignant cells, but it seemed to be more effective against them than against normal body tissues. On this last fortunate fact depends the successful treatment of cancer by radiation. It is the basis for radiotherapy, the new medical discipline which grew out of Roentgen's discovery.

The method is more subtle than may appear at first sight. Radiation does not just burn the cancer away. If the amount of radiation is carefully chosen it may be possible to kill the cancer cells while limiting damage to the surrounding normal cells, so that these eventually recover. As the cancer cells die they are carried away by the body's ordinary healing processes, and the hitherto rapid growth of the cancer is arrested. It stops growing, shrinks, and may disappear altogether. This may happen even if it is invasive, pushing its way between or through important body structures. In such cases radiotherapy may succeed where surgery would have been impossible.

Not all types of cancer can be treated in this way. Some are more sensitive to radiation than others. Body tissues also vary in their radiosensitivity. In favourable cases, however, radiation therapy can be entirely successful, either alone or in conjunction with surgery or some form of chemotherapy. Advances are continually being made, as new sources of radiation are developed and better methods to apply them are found.

It may puzzle the reader that radiation is so widely used to treat cancer when it is known that cancer can also be caused by radiation. There is no real paradox here, however. Penetrating radiation is a very harsh agent. As it passes through the cells of the body it causes damage of many sorts. In particular, there is damage to the machinery by which cells control their own growth and reproduction. In rare cases this system may be partly inactivated, leaving a cell no longer subject to the limitations on growth which control the life of normal cells. A cancer cell has then been created, and its growth and multiplication may eventually show up as a malignant tumour. Much more commonly the damaged cell is unable to grow properly, or cannot reproduce. It dies, and no lasting harm is done. The clinical results of many years of radiotherapy show that the chance of eliminating an existing cancer is much greater than the chance of inducing a new one. Even if one is induced, it too may be treated by radiotherapy.

Evidently, a favourable outcome is most probable if the exposure to radiation is high throughout the tumour but is as small as possible in the surrounding tissues. Much ingenuity has been applied to this central problem of radiotherapy.

One method of treatment is to direct a narrow beam of radiation into the tumour from outside the body, angling it from several different directions in turn. All beams are directed so as to pass through the tumour, where their effects add, but in reaching the tumour they pass through different volumes of normal tissue and so the damage to these tissues is small. This is the method of *teletherapy*, first done with X-rays but now usually done with the more penetrating gamma-rays from an artificial radioisotope. Cobalt-60 is most commonly used.

Teletherapy reaches a tumour deep within the body. If the tumour is near the surface, or is accessible through one of the body cavities, it may be possible to place a compact source of radiation on or within the tumour itself. Radioisotopes are used as sources of radiation for this purpose. Several sources may be combined so that the resultant radiation field is matched to the shape and

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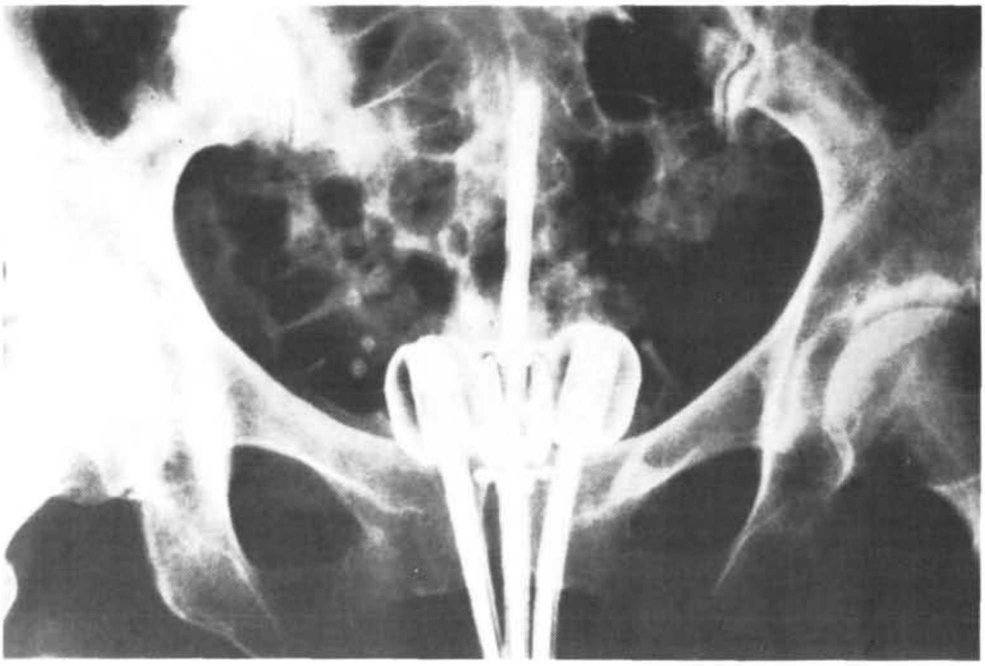


Radiograph showing an intracavitary plastic applicator in position for treating cancer of the cervix. The applicator has been loaded with three caesium-137 radioisotope sources through the guide tubes visible at the bottom of the picture (Royal Free Hospital, London).

size of the tumour. This form of treatment, known as *brachytherapy* or *curietherapy*, can deliver a well-defined dose to the tumour with minimum damage to the surrounding tissues, because of a useful property of small radiation sources: the radiation dose they deliver is intense close to their surface, but very much weaker only a few millimetres away. For this reason a carefully placed brachytherapy implant is one of the most effective forms of radiotherapy. As always, the aim is to give a large dose to the malignant tumour while sparing normal tissue.

Radium was the first radioisotope to be used like this. It was made up into "radium needles", which look like ordinary sewing needles but are thicker, about 1.5 mm, and are hollow. A typical radium needle is 30 to 40 mm long and contains a few milligrams of radium. The radiotherapist may push ten or more such needles into the tumour, in a carefully planned pattern with precise spacing. They are left in position for several days and are then withdrawn. For a surface tumour they may be mounted in a shaped piece of plastic or wax which is held in position against the skin. Such an applicator may also be shaped to fit inside a body cavity. It is designed to be effective against a tumour on or near the surface of the cavity.

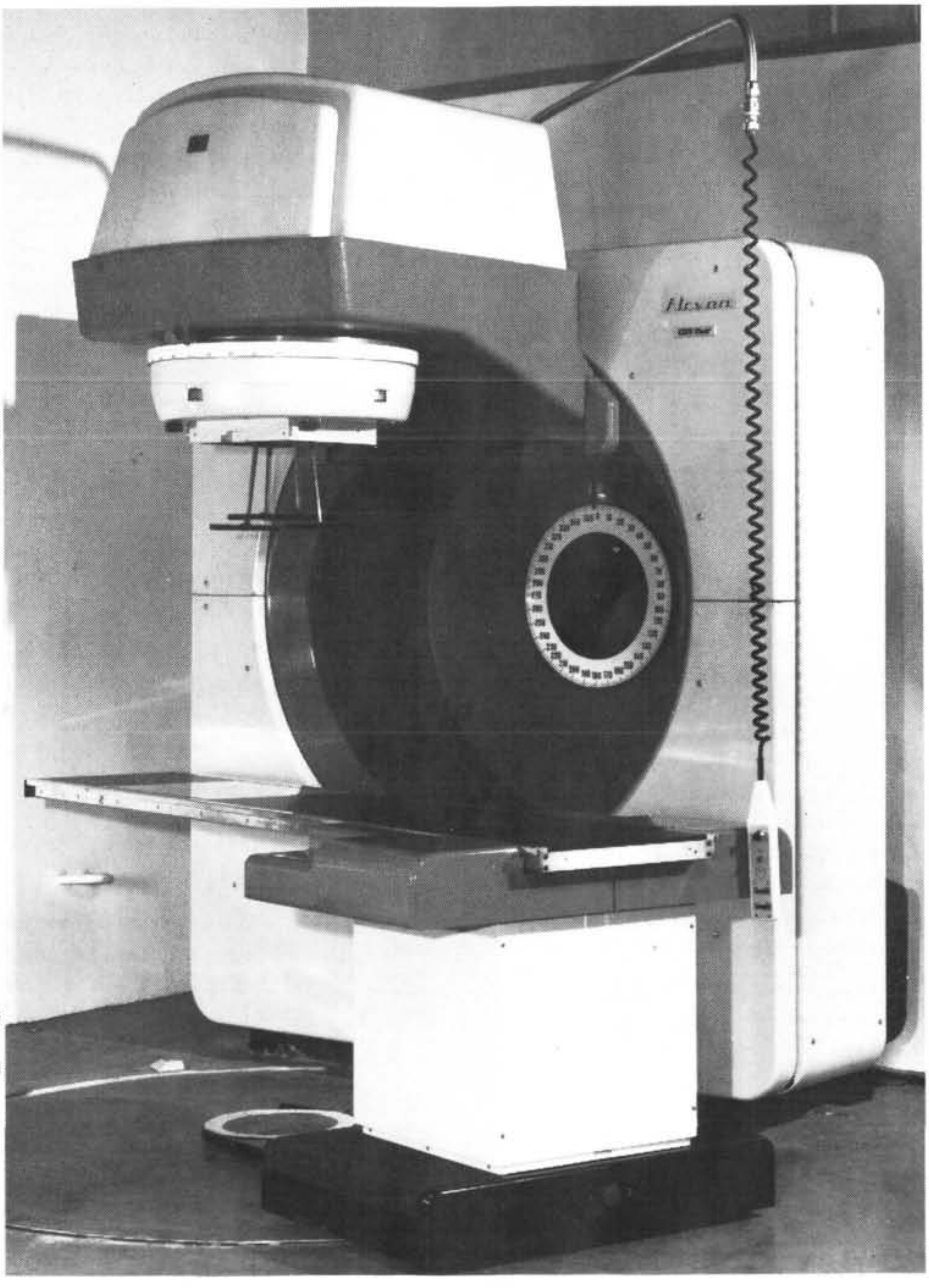
An important example of this last type of treatment is radiotherapy of cancer of the *cervix uteri*, the cervix being the lowest part or neck of the uterus. Squamous cell carcinoma involving the cervix is one of the commonest forms of the disease, amounting in many countries to nearly a third of all cases of cancer in women. Fortunately, the normal tissue of the healthy uterus is particularly resistant to radiation, so a high dose can safely be given. Simple standardized procedures for using radium sources to treat cancer of the cervix were developed during the early decades of this century. After constant study and improvement they still form the basis for the sophisticated treatments practised today.

Cancer of the cervix is a disease which attacks relatively young women, often at a time when they are still supporting their children in the home. There is thus an important sociological problem, in addition to the personal suffering involved. In the advanced countries the death rate due to this condition is decreasing, as greater awareness among women and other social improvements lead to earlier diagnosis, which is always important in the treatment of cancer. In the less advanced countries, on the other hand, these developments lag behind, and many cases of uterine cancer remain untreated. The question therefore arises, whether the methods of treatment now used in the advanced countries could be transferred successfully to the very different social and medical environments in other parts of the world.

In the modern methods which have been developed from the original radium treatment, an artificial radioisotope replaces the radium and teletherapy is often used as well, for example if the disease has reached an advanced stage and has spread away from the immediate neighbourhood of the cervix. In the early systems of treatment the radium sources were placed in position with forceps and were held in place by packing surgical wadding around them, a procedure which exposed the radiotherapist to a considerable dose of radiation. Nowadays an *afterloading* technique is used instead. The therapist places an empty plastic applicator in position near the entry to the uterus and only after this has been done are the radioactive sources loaded into the applicator. This can be done in a few seconds, with very little exposure to radiation.

Afterloading is a significant advance. It has become possible because artificial radioisotopes can be made much more intensely radioactive than radium, so that a source of the same radiation strength can now be very much smaller. A powerful radioisotope source may be little larger than the point of a pencil. It can be permanently sealed into the end of a flexible metal probe and by this means can be pushed through a fine plastic guide tube into its position in the applicator. Radium sources were too bulky for this.

The treatment of cancer of the cervix begins with a thorough medical examination of the patient and a histological investigation to confirm the nature of the tumour, its malignity, and its radiosensitivity. The plastic applicator is then placed in position, usually under general anaesthetic. Radiographs are taken to establish the exact location and orientation of the applicator in relation to adjacent body structures, and if necessary the positioning is corrected. The patient is then transferred to a ward where she stays for the one or two days required for the radiation treatment. The active sources are brought into the ward in a storage device, a lead cylinder weighing a few kilograms, which can be carried to the bedside. The therapist selects one source at a time, pushing the flexible probe in which it is mounted through a guide-tube into the applicator. This is *manual afterloading*. The number of sources to be loaded is usually three.



Teletherapy equipment for cancer treatment. The massi radiation shield at the top contains a cobalt-60 radiation source. A narrow beam of radiation is directed downwards to pass through the tumour. The shield can be rotated about the patient so the beam enters the body from different directions (GGR-MeV, Paris).

Information gained from the radiographs may be used as a basis for calculating the distribution of dose around the sources. As a result of this calculation the therapist may decide to modify the treatment plan, altering the period of irradiation or unloading the sources at different times.

Nowadays the storage container may be part of a semi-automatic device mounted on a trolley which is wheeled into the ward. This is placed at the foot of the patient's bed and is connected to the applicator by plastic tubes, through which the sources can be moved by flexible cables or compressed air. This is *remote afterloading,* controlled by a keyboard on the trolley. The operator is exposed to still less radiation, and so are nursing staff, as with this system the sources can easily be removed and replaced whenever the patient needs attention. Against this, the equipment is expensive and there are more things to go wrong.

With either method it is usual to repeat the treatment after a period of about one week without radiation. The tumour, which does not have a well-organized blood supply, recovers more slowly from the first dose than do the healthy tissues around it. As the cancer cells which have died are cleared away by the healing process the remaining cells are exposed to a better supply of blood, but this now acts to their disadvantage. If the fractionation has been correctly timed they will be growing rapidly when the second course of radiation is given, and in this condition they are particularly sensitive to damage by radiation.

After a further rest of two or three weeks the patient may be given a course of teletherapy, depending on the extent to which the disease has spread. Again, the irradiation is given in successive fractions.

To plan and carry through a course of treatment of the type described requires a well-equipped hospital and the co-operation of staff qualified in several disciplines. In an advanced country these will be a gynaecologist, a radiotherapist, and a medical physicist, working together in the radiotherapy department of a major hospital. In a developing country this may not be possible. There are few such hospitals, and the journey to reach one may be altogether too difficult for the patient. This is a world-wide problem which has been the concern of an international working party* of radiotherapists who have specialized in this field. The conclusions of this group form the basis of a project now being initiated jointly by the IAEA and the World Health Organization.

It is a recommendation of the Working Party that wider use should be made of manual afterloading, using the radioisotope caesium-137 instead of radium. Some early cases of cancer of the cervix can be treated successfully by this method alone, but when the disease is further advanced it may be necessary to use cobalt-60 teletherapy as well. Thus although much advantage can undoubtedly be gained by using simple intracavitary equipment to treat selected patients in hospitals close to their homes, it is also necessary to consider the interrelationship between central and local hospitals and the possibility of transferring patients between them.

It is evidently important that a project aiming to enhance the use of manual afterloading should be securely founded in a central hospital of high standard, with all necessary medical and administrative infrastructures, and that planned co-operation with other hospitals should take full account of local factors, including the transportation network, the availability of teletherapy equipment, regulation and practice relating to radioactive materials, and the types and degree of expertise already available. Full commitment to the project by the medical establishment of the host country, at all levels, will be essential.

The first project under the IAEA/WHO scheme is to be based in Egypt at the Kasr el Eini Hospital, Cairo, under the leadership of the Director of the hospital, Professor M. Mahfouz. A demonstration clinical unit will be set up in this hospital, with manual afterloading equipment chosen for simplicity and reliability. Treatment protocols and radiation-dose planning procedures are being written.

A number of training courses for medical staff from other hospitals in Egypt will be arranged by Kasr el Eini, the first such course being scheduled in the autumn of 1983. The project will then undertake to provide manual afterloading equipment to outlying hospitals, whose staff have received training at Kasr el Eini. A local brachytherapy unit could be thus established and staffed with trained personnel.

The scheme will subsequently be considered for further extension to hospitals in neighbouring countries. Funding for the first project in Egypt has been provided by the Government of Italy under a Technical Co-operation Agreement with the IAEA.

* International working party for the treatment of cancer of the uterus in developing areas using radium substitutes and afterloading techniques, an independent group sponsored by IAEA and WHO.