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# Introduction

The information in this book aims to help survivors of childhood and adolescent cancer to understand the many different aspects of long term effects of disease and treatment and the need for long term follow-up. This information may also be helpful when giving details of treatment to other doctors. It is not, however, intended as a substitute for individual medical care.

## INTRODUCTION

Treatment for cancer during childhood or adolescence can be a complex and long process. Depending on the age of the child at the time of diagnosis, little detail of the original diagnosis or treatment may be remembered or recalled. Those who were older when their illness occurred may have clear memories of what happened at the time but may not understand some of the possible later effects of treatment.

Many individuals who have successfully completed cancer treatment have been followed up regularly for several years after treatment was completed. They may have had the opportunity of learning more about their cancer and its treatment from parents and doctors.

Young people often wonder about the need for ongoing follow-up, particularly if all seems normal and if no specific problems related to past treatment have been detected. Why is it so important to know now?

Over the past 30 years the cure rate for children and adolescents with cancer or leukaemia has markedly improved. Approximately 80% of children and young adolescents currently diagnosed with a malignancy can expect to be cured. Some childhood cancers such as acute lymphoblastic leukaemia have achieved a 90% five year survival and yet research tells us that only about 70% of childhood cancer survivors have accurate knowledge of their diagnosis, and treatment, and only a third when asked, knew that there could be health problems in the future, related to past treatment.

As survival has increased, so has the recognition and knowledge of long term effects of cancer and its treatment, some of which may not become apparent for many years after treatment is completed. These health problems may be physical and there may be problems with memory and learning, or the illness may have been so stressful that emotional problems persist.

Participation in an appropriate long term follow-up program is increasing awareness and understanding of potential problems that might arise as a result of cancer and its treatment. Such follow-up programs are also designed to recognise and manage problems as they occur, to assist with decisions about general health and plans for the future, provide a means of screening for potential future health issues, and to provide advice about things that can be done to help the person who has survived childhood cancer and its treatment stay as healthy as possible.

Part or all of some sections of this book may not be relevant or apply to every person, because treatment regimens have changed over the years and are different for each type of illness.



To try and make this book a little less difficult to read, the different types of treatment have been divided into separate parts although in reality many overlap.

Knowing the type of treatment that was given in the past will help this book be used more effectively. If treatment details are unknown or unclear the doctor or nurse coordinator can be asked to fill in the Treatment Summary in the Appendix at the back of the book.

It is hoped that this book will be a useful and supportive resource for survivors of childhood cancer and their families and that it will also provide valuable information for health professionals and others involved in their care.



# Types of cancer treatments

Chemotherapy, surgery and radiation therapy or a combination of some of these are used in the treatment of nearly all childhood cancers. Not every patient needs all types of treatment. The nature of management is different for each different type of cancer and often even for different patients with the same type of cancer. These treatments can be associated with long term effects or with new problems that may occur for the first time many years after the original cancer was treated. However not every patient who has had cancer treatment will experience problems and the extent of the long term effects may vary in different people.

## TYPES OF CANCER TREATMENTS

### Surgery

**Surgery is an important component of treatment for many but not all cancers.**

In almost all patients, a central venous catheter (CVC) will have been inserted when the cancer was first diagnosed, to make giving chemotherapy and other drugs easier. In some patients, after the CVC was removed there remains a small 'cuff' of material which can be felt under the skin close to where the CVC removal site was located. This does not need to be removed but can be easily done if needed. Some patients, when they feel their neck, have the impression that the CVC is still present. This is due to fibrous tissue causing scarring around the neck vein where the CVC was placed, and in most cases will gradually resolve. It is of no significant concern but if you are worried, you should ask your doctor.

In some patients surgery may involve taking a small piece (biopsy) of tumour to make a diagnosis. Others may require removal of the whole tumour. Occasionally tissue surrounding the tumour, a whole organ (for example a kidney) or part of a limb may need to be removed if cancer is present in that area. It is quite possible to remove part of an organ, or one of a pair of organs without affecting function. It is, however, important to take into account the effect that an individual's chemotherapy or radiation therapy program might have on the remaining organ or tissue.

**Chemotherapy, surgery and radiation therapy or a combination of some of these are used in the treatment of nearly all childhood cancers.**

In some instances the best possible surgery for cure of the tumour may have resulted in significant changes in physical appearance or in function of the area of the body that was treated. Fortunately there have been major advances in plastic (cosmetic) surgical techniques which can do much to improve such problems. Prosthetic technology has also resulted in more functional artificial limbs in those who require them. It is important to discuss concerns about appearance or function of a damaged area with your doctors. Advice on further management to improve appearance and/or function of the affected body area may be available.



## TYPES OF CANCER TREATMENTS

### Chemotherapy

Treatment with anti-cancer drugs is a vital component of management of almost all cancers and leukaemias occurring in children and adolescents.

There are many different types of chemotherapy drugs that act in different ways, in different parts of the cell, to kill cancer cells. Chemotherapy can be given into a vein (intravenously), into muscles (intramuscular injections), under the skin (subcutaneous injections), by mouth (orally as tablets or liquid suspension) and into the spinal fluid (intrathecal). All the different drugs, no matter how they are given, ultimately stop cells dividing and growing, with the essential aim of killing cancer cells.

Anticancer drugs also have effects in many normal cells of the body. Generally those cells which multiply most rapidly are more likely to be affected; for example hair cells, cells lining the gut and bone marrow cells. Normal cells have a much greater ability than cancer cells to repair damage caused by chemotherapy drugs. This allows treatment to be given repeatedly, with the aim of having more effect on the cancer than normal cells.

Many of the most effective drugs do have unwanted side effects. These can happen during treatment (eg. low blood counts, mouth ulcers, hair loss). Other drugs cause irreversible problems even when treatment is finished (ie. high tone deafness after treatment with cisplatin, reduced fertility after high doses of Cyclophosphamide, or reduced heart function after Doxorubicin).

Normal cells have a much greater ability than cancer cells to repair damage caused by chemotherapy drugs. This allows treatment to be given repeatedly, with the aim of having more effect on the cancer than normal cells.

The total dose of the drug given, the combination of drugs used (some drugs have an additive effect) and whether radiation treatment was also given are all important in determining if there are any health problems after treatment has finished. People vary in the way their bodies respond to these treatments and in the type and amount of side effects that may happen.

## Radiotherapy

Radiation therapy uses high energy X-ray beams aimed at a tumour, to kill tumour cells. The cells are killed by damage to the DNA in the nucleus (the command centre) of the cell. Some cells die immediately while others die when they next attempt to grow.

Although the X-ray beams are aimed as accurately as possible at the tumour, the beams pass through normal tissue on their way to and from a tumour within that tissue. In the process, normal tissue cells can also be damaged. However these normal cells have a capacity to repair themselves, unlike tumour cells. The extent of damage and the extent to which full repair can occur in normal tissues depends on a number of factors.

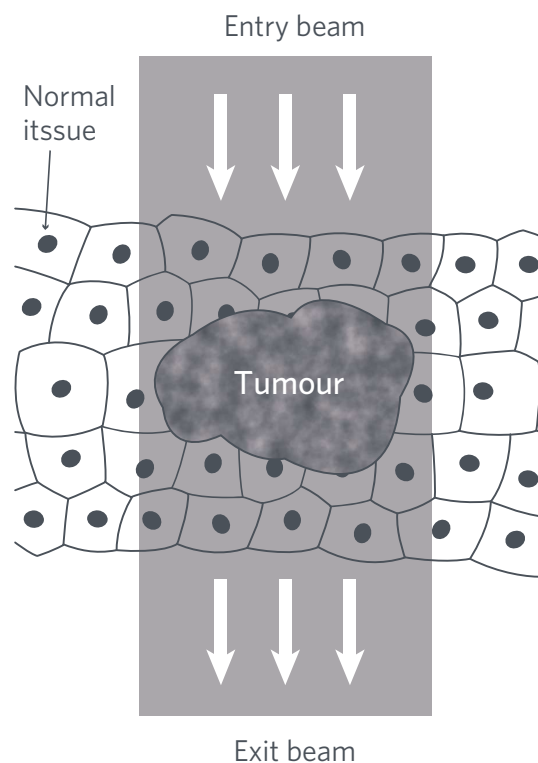
Radiation therapy uses high energy X-ray beams aimed at a tumour, to kill tumour cells.

Growing cells are more sensitive to radiation. The sensitivity of a particular tissue depends not only by the type of tissue but also on where it is in its growth cycle, which in turn depends upon the age of the person being treated. For example the brain grows rapidly from birth to approximately four years of age. The rate of brain growth slows in the older child and

adolescent. Reproductive tissues such as breasts, ovaries and testes change little in early life and develop rapidly just before and during puberty.

The volume (amount) of the tissue given/exposed to radiation and the dose it receives, as well as additional effects from other treatments like chemotherapy and surgery, can all influence the risks for long term damage.

The normal function of the hypothalamus and pituitary gland and the effects of damage of these areas will be discussed in the next chapter.



**FIGURE 1.** During radiation treatment, X-rays aimed at tumours also pass through normal cells





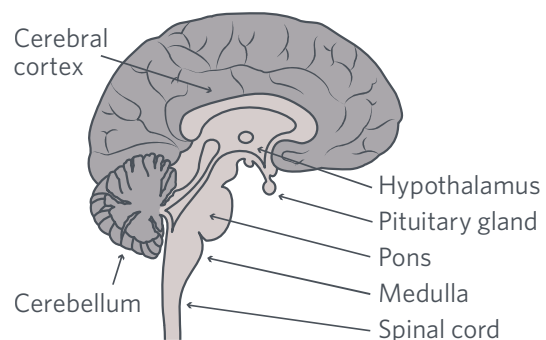
# Brain cancers and their treatment

## BRAIN CANCERS AND THEIR TREATMENT



Cancers can occur in any area or part of the brain and in the brain stem. Surgery is an important component of curative treatment for most brain tumours, as is radiation therapy.

Chemotherapy is being used increasingly in children with brain tumours. Radiation treatment for brain tumours may include only the part of the brain in which the tumour is situated, the whole brain, or the whole brain and spine. Some patients with leukaemia require whole brain irradiation.



**FIGURE 2.** Anatomy of the brain showing position of the different parts

## Late effects of treatment

The late effects depend on the amount of brain treated, the part of the brain treated (if not the whole brain), the dose used and the age of the patient at treatment. It is important to remember that there may also be effects of the tumour itself and interaction with other treatments.

The brain grows and matures very rapidly in the first four years of life and is most vulnerable to potentially damaging treatments during this phase. Some problems become apparent within a few years of treatment. However in children, particularly those under the age of five years at the time of treatment, problems with concentration, short term memory, and learning difficulties, collectively known as neurocognitive problems, may become more obvious as the child progresses through school.

Older children and adolescents may have difficulties in the final years of high school and tertiary education. Neurocognitive problems causing learning difficulties occur as a result of radiation to the whole brain, with high dose Methotrexate or Cytarabine and with intrathecal chemotherapy. Girls are at higher risk than boys. There is increasing evidence that surgery also affects neurocognitive function in some children.

Growth and development from childhood into adulthood can be altered if the hypothalamus and/or pituitary gland are affected. These issues are discussed in detail in the following chapter.

## Recommendations for screening and follow-up

Special neuropsychological testing can help to assess problems. This type of testing may need to be repeated at intervals so that information is available for teaching staff, to help plan learning strategies most suitable for the child or adolescent.

Baseline neuropsychological evaluation should be done for all children who receive treatment that may impact on neurocognitive function. Following this, a recommendation for repeat testing may be made and should be done at key transition times (early primary school, into Year 7 and before Year 11). Liaison with the school is important so that specific interventions and help can be applied, appropriate extra funding through state government can be sourced and that appropriate career and vocational plans are made. This specialised help will aid education, job support and independent skills for the future.



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# The pituitary gland and hypothalamus

## THE PITUITARY GLAND AND HYPOTHALAMUS

This section will focus on pituitary hormones and will discuss how each hormone loss affects the body, how problems can be detected and management of hormone failure, if it occurs.

The pituitary gland is a small, pea shaped structure, situated underneath the brain. It is comprised of two parts – the anterior (front) lobe and the posterior (back) lobe.

These parts are connected by a stalk to an area of the brain called the hypothalamus, which controls pituitary gland function via chemical messages. The pituitary gland in turn controls the functions of the hormone-secreting glands in the body by releasing a series of its own hormones into the blood circulation.

A hormone is a chemical messenger that is made in one part of the body and carried via the blood stream to another part of the body where it carries out its effects.

The anterior lobe of the pituitary gland makes a number of hormones, including growth hormone. Some of these hormones control other hormone-producing glands in the body, such as the thyroid, adrenal and sex hormone glands (ovaries and testes). The posterior lobe makes a hormone involved with the retention of normal water and salt balance in the body. The complex pathways of these hormones and their effects on the body are summarised in Figure 3. Deficiencies of these hormones can occur as a result of all forms of cancer treatment – surgery, chemotherapy and radiation therapy.

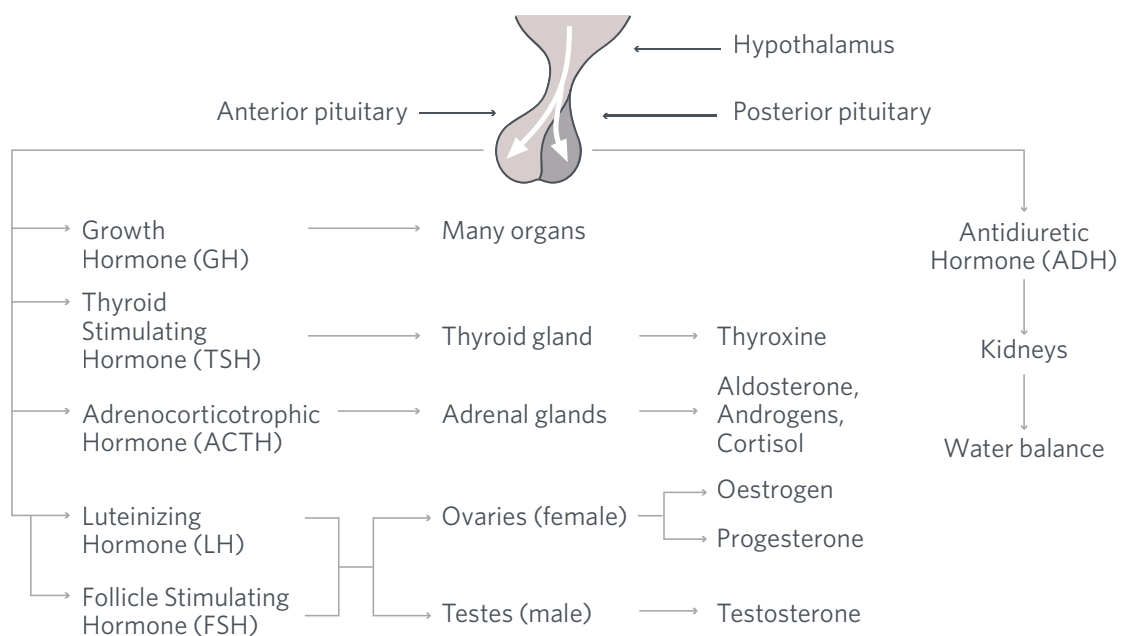
It is important to understand that the process of radiation damage to the pituitary gland is indirect and can be very slow. It may take up to 20 years after radiation treatment for the full spectrum of hormone deficiencies to evolve. During this long period, a person may have times of being completely normal and times when the levels of some hormones may change from high to low and finally may disappear completely.

## Damage to the pituitary gland and hypothalamus by cancer or its treatment

A tumour itself and/or surgery to that tumour can damage the pituitary gland. The anterior lobe of the pituitary gland is very sensitive to the effects of radiation treatment and one or more of its hormones frequently stop functioning in the years after radiation therapy.

The posterior lobe is not damaged by radiotherapy. However, some children and adolescents who have had damage in the region of this gland, due to a brain tumour, may experience problems of water control, caused either by the position of the tumour itself or by necessary surgery in the area.

Damage to the hypothalamic-pituitary area may occur either due to the size or position of a tumour or as a result of its treatment.



**FIGURE 3.** The normal function of the hypothalamus and pituitary gland and the effects of damage of these areas will be discussed in the next chapter





# General factors influencing development

## GENERAL FACTORS INFLUENCING DEVELOPMENT

**Normal growth is dependent upon a combination of adequate nutrition, normal growth hormone and growth factors, and bones that can respond to these messages.**

Growth differs among normal children, partly depending on the size of the parents and any problems that may have occurred around the time of birth (such as low birth weight). Growth also depends on general health and whether weight gain has been normal. The timing of puberty in family members is likely to follow a similar pattern so that if a parent, brother or sister had early or late puberty, another child in the same family is likely to follow a similar pattern.

Cancer treatment may result in weight loss and a period of associated poor growth, if the individual is very ill during treatment. Many children and adolescents, however, grow quite normally during treatment. Growth is regularly charted throughout the time of cancer treatment and compared to the normal growth rate of children and adolescents of similar ages. Changes from previous growth rate can thus be detected with time.

Poor growth, generally due to poor nutrition and ill health, usually improves when chemotherapy is ceased and 'catch up' growth occurs.

Children who have had tumours in certain areas of the brain and those who have had radiation therapy to the whole brain, to the region of the pituitary gland, or to bone or muscle tumours of some regions of the head are at risk of reduced pituitary function. Radiation treatment to the head and/or neck may affect the thyroid gland. Absent

or low production of normal hormones, essential for growth, will result in slowing down of a previously normal growth pattern. Hormone deficiencies can be identified and treated to improve growth rates in children and young adolescents.

Radiation treatment to bones results in reduced bone growth that is not overcome by the effect of hormones. Final height is affected by both hormone deficiencies and bone growth.

### Growth hormone

**Growth hormone is made in the pituitary gland at the base of the brain. Growth hormone (GH) is released in variable amounts over 24 hours, especially during sleep and exercise.**

Once released from the pituitary gland, GH travels via the blood stream and acts on several other tissues around the body including liver, kidneys and bones. Growth hormone interacts with an insulin-like growth factor which combines with growth hormone to promote growth and alter muscle metabolism. Growth hormone also plays a part in the control of blood sugar levels.

A child or adolescent who has a deficiency of growth hormone will not grow normally. The growth rate will gradually fall away from the 'before treatment' position on the growth chart, alerting the doctor to the

possibility of growth hormone deficiency. The child may feel very tired and may notice a tendency to have a 'plump', more rounded abdomen.

Adults with growth hormone deficiency may feel chronically tired. Subtle changes occur in heart function, lipid levels (cholesterol and other fats) and in bone quality. Adults may have no symptoms. The effects of GH deficiency on bones and cholesterol are not usually noticed or felt by a person, although they have potential serious effects on health. On the other hand some young adults with GH deficiency may have emotional symptoms such as tiredness, irritability, decreased sex drive and increased feelings of being anxious.

Diagnosis of GH deficiency is complex and needs to be undertaken by a specialist endocrinologist.

## Assessment of growth and detection of possible growth hormone deficiency

**Regular, accurate measurement by the same measurer, using a properly set up, counterbalanced measuring device, will accurately detect the growth pattern in any child.**

Any deviation from the normal rate of growth will be seen when the growth pattern is plotted on a graph which demonstrates normal growth patterns for a normal population. If growth rate is slowing down, further assessment is made for possible causes.

Basic blood tests may need to be performed when a child is first assessed with growth problems. More complicated tests for growth hormone production may then be required.

Because growth hormone is produced at different rates during 24 hours of the day, it cannot be accurately or reliably measured as a single blood test. It is therefore necessary to do a stimulation test to check the ability of growth hormone to respond to stress. Normally, two tests are necessary to completely check for a deficiency of growth hormone.

As normal growth is also affected by sex hormone levels, it is important to establish the maturity of a young person's bone development. An X-ray of the left hand (called a 'bone age') is used to help with an assessment of true biological age. Bone growth does not always progress at the same rate as the child's age. If a child has early puberty, the bone age will be generally older than the child's age. In situations where puberty will be late, the bone age will be younger than the child. This leaves more time to grow and does not indicate anything wrong with the bones themselves.

## GENERAL FACTORS INFLUENCING DEVELOPMENT

### Information about growth hormone treatment

Growth hormone has been successfully used as treatment for growth hormone deficiency for over 50 years. Modern growth hormone is a biosynthetic hormone, not a human product.

Before modern growth hormone (made by recombinant DNA technology) was available, human pituitary glands taken at autopsy were the source of growth hormone. The use of this hormone was later found to carry a small risk of a virus-borne infection. This does not occur with modern growth hormone.

Long term follow-up studies in many groups of children and adults who have been treated with GH show no evidence for an increased risk of cancer recurrence, (timing or rate of recurrence) or in the type of tumour that might return in patients who have been treated with growth hormone, compared to patients who have never been treated. It is recommended however, that all children who have received GH, in particular cancer survivors and those receiving GH in adulthood, should be in surveillance programs.

Some studies have shown a slight increase in lifetime risk of a meningioma (a benign tumour of the coverings of the brain that can usually be removed surgically), in people who have had growth hormone treatment compared with those who have not. However it is known that radiation increases the risk for a meningioma and it is likely that those people who have growth hormone deficiency are also those who have received the highest dose of radiation.

In general, where growth hormone deficiency occurs as a result of cancer treatment, the Federal Health Department in Australia requires that a child must have completed cranial irradiation and chemotherapy at least one year prior to consideration for growth hormone treatment and that a brain scan (MRI) is stable or clear of tumour, before such treatment can be approved.

It is recommended that all children who have received growth hormone, in particular cancer survivors and those receiving growth hormone in adulthood, should be in surveillance programs.



## Growth hormone treatment for a child

Growth hormone treatment is used for the purpose of improving growth and catching up growth that has been lost during the time of deficiency. The aim is to improve final adult height.

Growth hormone is given by injection under the skin on a daily basis. Response to treatment is monitored every three months. Growth hormone is ceased if the child or adolescent fails to respond to a six to twelve month course of treatment with a significant increase in growth rate. There is obviously no point in continuing treatment that is not effective. It is also stopped at any time if the parent and/or child definitely wish to cease treatment.

## Growth hormone treatment for an adult

Growth hormone treatment may be indicated for adults who are growth hormone deficient, for maintenance of health and well-being, lipid profile, heart function and bone quality (for prevention of osteoporosis).

At the present time, the government in Australia has approved the use of growth hormone for deficient adults but it is very expensive and as yet there is no financial assistance to increase availability for those needing treatment.

## GENERAL FACTORS INFLUENCING DEVELOPMENT

### Thyroid stimulating hormone

Thyroid stimulating hormone (TSH), made in the pituitary gland, stimulates the thyroid gland (in the neck) to make metabolic hormones, that help control the normal rate of function of each cell in the body.

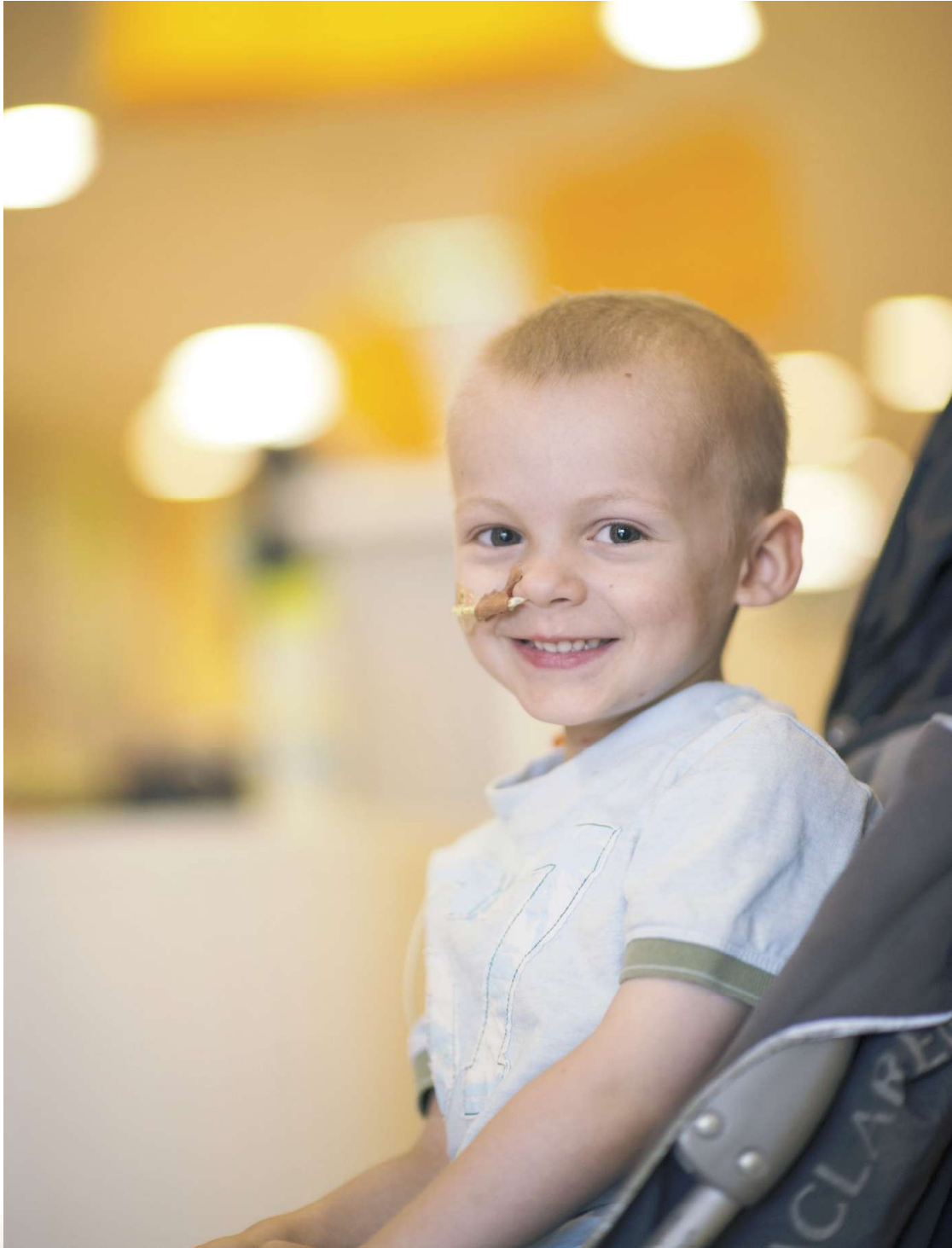
Following cranial irradiation, the TSH normally produced in the pituitary gland may be lacking or produced in insufficient quantities. As a result the thyroid gland receives less stimulation and levels of thyroid hormone are reduced.

When spinal irradiation has been given as well as brain irradiation, for some types of tumours, the thyroid gland itself may also be directly damaged. Assessing the effect of combined damage at the level of the pituitary and to the thyroid gland itself can be difficult and requires a test of both the TSH and the circulating thyroid hormones, in order to obtain an accurate picture of the situation.

It is impossible to detect a mildly under-active thyroid by just looking at a child or adult. Thyroid hormone levels are therefore measured each year. If the growth rate is becoming slower in a child, this may be a sign of low thyroid hormone levels.

In general, a simple blood test is sufficient to determine the state of the thyroid gland. If the levels of thyroid hormone are low, a small tablet of a synthetic thyroid hormone (thyroxine), identical to that which is normally produced in the body, can be used to replace the missing hormone. This will result in an affected person feeling back to normal again. The tablet is not associated with any side effects whatsoever and can be used throughout life without any danger. Blood tests are required every six to twelve months to monitor whether the dose is appropriate. Adjustments may be needed as a child grows.

If the growth rate is becoming slower in a child, this may be a sign of low thyroid hormone levels or of growth hormone deficiency.



## GENERAL FACTORS INFLUENCING DEVELOPMENT

### Gonadotrophins

**Gonadotrophins—follicle stimulating hormone (FSH) and luteinising hormone (LH) are produced by the pituitary gland and travel to the ovaries in a girl or testes in a boy.**

They give a message to stimulate the onset of puberty and, later on, to maintain normal adult sexual characteristics and sex hormone production.

Depending on the age at which these hormones may be lost, following radiation to the brain, lack of, or absence of, these messages will lead to failure to enter puberty or failure to progress through puberty or to later loss of previously normal adult sex hormone levels.

### Gonadotrophins and puberty

**The hypothalamus, an area of the brain, located at the base of the brain above the pituitary gland, normally holds back or inhibits the onset of puberty until late childhood.**

When this area of the brain is damaged, however, this natural inhibition is lost, allowing puberty to commence at an earlier age than usual.

Puberty occurs on average two years earlier in both boys and girls following cranial irradiation. In girls, the average normal age of starting puberty is around eleven years, but after cranial irradiation it is quite common for puberty to start around 8½–9 years. For boys, puberty is

usually seen most obviously around the age of 13 years (although testicular enlargement can occur a little earlier). After cranial irradiation it is quite common for boys to start development of puberty at the age of eleven years.

**Changes of sexual development are rapidly obvious in girls and boys. Usually the first sign of puberty in a girl is the presence of breast development. For boys the first sign of puberty is enlargement of the testes (testicles).**

## Importance of long term follow-up

There are a number of important reasons for regular follow-up of growth and development, particularly because most parents and adolescents believe that everything is normal once growth and puberty commence.

- Children who have true precocious (very early) puberty, after cranial irradiation, often also have growth hormone deficiency. Because puberty makes a child grow faster and growth hormone deficiency causes slow growth, the combined growth pattern may look 'normal' but the child will not reach his or her expected final height unless all hormones are normal. These problems need to be detected early.
- Although gonadotrophins and puberty may 'switch on' early after cranial irradiation, there is usually a gradual loss of these hormones over eight to ten years. The levels may eventually become so low that sex hormone replacement treatment may be needed.
- If radiation has been given at a very early age, gonadotrophin function may be completely lost and puberty may not happen at all until suitable hormone replacement treatment is initiated.

## Loss of gonadotrophins in girls

After radiation to the hypothalamic pituitary area, inadequate amounts of gonadotrophins may be produced. In girls this means the ovaries stop receiving signals.

A girl with this problem either fails to enter puberty or her body ceases to make oestrogen, depending upon the age at which the problem commences. Periods, if occurring, initially become irregular then stop altogether. This should prompt a visit to the doctor and a question as to whether damage of the pituitary gland may be causing this change. (For further discussion about female sexual function see chapter beginning on page 65).

Sometimes however, young people who have had a serious illness in the past do not question this type of apparently mild abnormality and do not seek medical help. Unfortunately, if this problem is missed and the pituitary gland has ceased to signal to the ovaries to make oestrogen, the affected person will eventually develop severe osteoporosis at a relatively early age, such as in the mid 20s to 30s. Other, more subtle changes also occur due to oestrogen deficiency, such as accelerated aging of skin, loss of muscle tone, poor lipid profile (cholesterol and other fats, which can then have an effect on heart function), but these problems are not usually obvious to the patient until they have been present for many years.

## GENERAL FACTORS INFLUENCING DEVELOPMENT

### Loss of gonadotrophins in boys

Radiation to the hypothalamic pituitary area at an early age may cause complete failure of gonadotrophin messages to the testes. Puberty will then fail to occur until introduction of suitable hormone replacement treatment.

For boys who have started puberty early as a result of radiation treatment to this area, it is even more difficult than in girls to detect a gradual loss of gonadotrophin function and loss of sex hormone. There is no obvious marker of 'normality' for boys (such as regular periods for girls).

Sexual function can continue to be normal, even at extremely low levels of male hormone (testosterone). This is a fact that is not commonly recognised by many people and most boys believe that normal sexual function equals normal testosterone. Similarly, libido (sexual interest) is not determined solely by the level of testosterone and therefore may not be a good guide to hormone levels in the adolescent male. It is quite possible for a young man to lose a great deal of his normal hormonal function while being completely unaware of the abnormality. He may feel a little tired but, unlike girls with problems of puberty development, he is unlikely to seek medical advice.

The size of the testes is determined largely by sperm producing cells. It is quite possible to have absolutely normal adult male hormone levels (testosterone) but very small testes after brain irradiation

and/or chemotherapy. However when radiation has been used locally to the testes (for leukaemia relapse or during whole body irradiation before bone marrow transplant) testosterone production is also frequently damaged.

A decrease in normal FSH and LH production after brain irradiation can be accompanied by a decrease in testis size over time. Although this phenomenon may be very obvious to the doctor, it is not a feature that is usually obvious or considered by an affected boy.

These complicated issues will be discussed further in the section on male sexual function following chemotherapy and bone marrow transplant (see page 73).

It is quite possible for a young man to lose a great deal of his normal hormonal function while being completely unaware of the abnormality. He may feel a little tired but, unlike girls with problems of puberty development, he is unlikely to seek medical advice.

## Adrenocorticotrophic hormone

The pituitary gland normally produces a hormone, adrenocorticotrophic hormone (ACTH), that stimulates the adrenal gland to make cortisol. Cortisol is a stress hormone, keeping the body 'safe' during periods of acute physical stress such as acute medical illness, surgery, fracture or any other major bodily insult.

Over many years following radiation to the hypothalamic pituitary area, the production of this very important hormone often decreases. The changes are subtle and most patients do not recognise an abnormality in their daily function. However the ability of the body to respond to physical stress may gradually decrease and the condition may only become obvious during a completely unexpected event, such as acute appendicitis or a motor vehicle accident. The affected person might have a sudden serious collapse with low blood pressure at those times. This type of event is potentially dangerous and is both alarming and very unpleasant for an affected person. For this reason it is advised that a routine blood test for cortisol production be performed each year for those patients who have received brain radiation to the hypothalamic-pituitary area.

If cortisol deficiency has been established with an appropriate blood test, the affected person may need to have permanent replacement treatment with cortisone (cortisol) tablets, usually given twice daily.

For added safety, it is usually advised that if a person has any other evidence of pituitary hormone problems (such as growth hormone deficiency) it should be assumed that he or she might not be able to respond to a serious physical stressful event (adrenal crisis). That person should therefore be given information about the possibility of such a crisis and how to manage a stress situation if it does occur.

## GENERAL FACTORS INFLUENCING DEVELOPMENT

This is a synthetic medication with no side effects for replacement treatment. In this case cortisone is simply a replacement for the missing cortisol. It does not cause a person to become overweight, does not cause osteoporosis and does not cause other side effects (normally associated with the intake of relatively large amounts of cortisone for treatment of other conditions such as arthritis or asthma). Replacement cortisone does not cause suppression of the immune system of the body.

If a person has no ability to respond to stress due to lack of cortisone, it is essential to give an emergency dose of cortisone at the time of any general anaesthetic or other major health problem such as gastroenteritis, fever or accident causing a bone fracture. This cortisone is usually given as an injection and patients who need this type of treatment are carefully instructed by their specialist doctor. Specific details of when to administer cortisone, how to administer cortisone and who should administer cortisone will be given by the specialist doctor, together with instructions to any other medical practitioner who might be in attendance during an episode of acute ill health.

It should be emphasised, however that this type of problem ie. being unable to respond adequately to acute physical stress, does not affect every person who has received radiation to the brain.

If a person is completely lacking in normal cortisol production after cranial (brain) irradiation, he or she may become extremely tired and may need to have a sleep in the afternoon after returning home from school or work. General tiredness, lethargy and mild weight loss are all symptoms of cortisol deficiency. There may also however be symptoms of other conditions such as recurrence of the underlying condition of tumour or leukaemia. It is therefore very important to check with the doctor if any of these problems are present.

## Antidiuretic hormone

Antidiuretic hormone (ADH) is a hormone produced by the posterior (back) lobe of the pituitary gland. It is responsible for maintenance of normal water balance in the body. Loss of ADH from any cause is called diabetes insipidus.

It is important to note that this condition is not related in any way to diabetes mellitus, a condition in which blood sugar levels are high.

Some children and adolescents may have had a tumour in the area of the hypothalamus or pituitary gland and may suffer from diabetes insipidus as a result of the tumour itself or its surgical treatment.

Diabetes insipidus results in an inability of the kidney to retain water due to a lack of ADH message so large volumes of urine are passed. If there is only partial deficiency, the affected person drinks large amounts of fluid to make up for the losses. It may be very difficult to keep up with the fluid losses if there is a severe deficiency or if the weather is hot. The person can become at risk of dehydration and salt imbalance if denied access to adequate fluids.

A diagnosis of diabetes insipidus is established by seeing how concentrated the urine becomes after a period of fasting (for instance the first urine passed in the morning) and comparing blood and urine salt levels. If simple tests are inconclusive, a formal 'water deprivation test' is carried out under very close supervision, with blood and urine tests performed during a period where no fluids are allowed. The test is stopped before the patient becomes dehydrated.

If diabetes insipidus is confirmed, treatment is given by replacing the missing hormone, in the form of a nasal spray or tablets once or twice per day. Most patients prefer the tablets although very young children may be more easily managed with the nasal spray, until they can take tablets. The dose is adjusted so that thirst and urine output becomes normal. Treatment should be supervised by an endocrine specialist.



# Cancer treatment and other organs in the body

Cancers occurring in a particular site in the body may need local surgery and radiotherapy, with or without chemotherapy. Leukaemias and lymphomas affect many parts of the body and need systemic chemotherapy treatment. Other solid cancers are treated with a combination of chemotherapy and surgery, and in some cases localised radiation, to ensure long term cure.

These treatments may also have effects on normal tissues near (or adjacent to) the tumour site.

### Bone and soft tissues

Bones and soft tissues that have been treated with radiation therapy may grow less well than normal. The extent to which growth is affected depends on the dose of radiation, the amount of tissue treated and the age of the person at the time of treatment. The effect of such treatment on the growth of normal tissues become more apparent with time after treatment particularly during years when normal tissues grow quickly, as occurs during puberty.

If the treatment was given to a part of the face, chest or abdomen, the area treated may eventually appear slightly less well grown than the unaffected side, giving an asymmetric or unbalanced appearance. This is usually more apparent to the person himself or herself than to others, but if the effect is sufficient to cause concern, a surgical opinion regarding possible improvement with reconstructive surgery may be appropriate.

Radiation to an arm or leg can lead to that limb being slightly shorter and smaller than the opposite limb. Increased swelling due to fluid retention can sometimes occur in limbs after radiation. The use of stockings, elevation of the limb at night, orthotic shoe inserts, shoe heel inserts and other specialised fittings may be helpful.

Radiation to the spine can reduce its capacity to grow. Both early and late radiation to the spine leads to some loss in final height. If treatment has been early, there may be a loss of nearly 10 cm in final

height outcome by the end of adolescence. If treatment has been in later childhood, the loss may be closer to 4–5 cm.

If radiation is given at an early age (two to five years), growth effects on the spine can be seen by the time the child reaches puberty. As well as growth in the long bones of arms and legs, one of the main areas of growth during the late stages of puberty is an increase in the length of the trunk. When radiation has been given at an early age, this component of growth is considerably reduced, and the adolescent will have a definitively short trunk.

When radiation treatment to the spine is given at a later age, such as around eight to twelve years, the loss of spinal growth is less marked. This happens because the child has often already completed the growth spurt of puberty before radiotherapy damage to the growth plates of the spine has caused cessation of growth. These adolescents will not have obvious shortening of the trunk.

If the spine has lost some or all of its capacity to growth, an adolescent growth spurt does not occur. In this case, even when growth hormone is also being used, the appearance is of continuing growth without the increased growth rate expected during puberty. Families need to be aware that final adult height will be reduced in situations where spinal radiation has been given, even when growth hormone lack has been adequately replaced.

Radiation therapy to the spine may also affect the structures in front of the spine through which it passes, such as the

thyroid gland, the heart, lungs, breasts, bowel and ovaries. See discussion about effects on these areas later in the section.

Bones that have received large doses of radiation can become thinner and less strong as the person becomes older. These bones may be damaged or break (fracture) more easily if stressed. Assessment of bone quality can be made using a bone density test. However, nearly half of a person's bone mass for life is accumulated during puberty. As puberty may be late, or may need to be helped with medical treatment in an adolescent who has had cancer, interpretation of a bone density test should be made by a specialist. Otherwise an inappropriate diagnosis of 'osteoporosis' may be made, when the real issue is simply of delayed puberty.

Bones, muscle and other connecting tissues are not generally affected by chemotherapy. However, children and adolescents being treated for leukaemia, and patients who have graft versus host disease after a bone marrow transplant, receive corticosteroids such as Prednisolone or Dexamethasone) repeatedly and sometimes for a long time. These steroids tend to leach calcium from the bones, making them more fragile. Methotrexate (a chemotherapy drug) may interact with calcium metabolism, and also affect the strength of bones. When bones become fragile, crush fractures may occur in the spine. Occasionally there may be reduction in the blood supply to growing ends of bones (avascular necrosis), resulting in partial collapse of these bones, which, in turn, makes bone surfaces irregular. Arthritis may then develop. Surgery such

as a hip replacement may eventually be necessary if there is pain or very limited movement of an affected joint. This is unlikely to be performed until growth is complete.

Adolescents with a primary bone tumour involving a limb may have had an amputation or limb conserving surgery. This involves the removal of the affected bone and replacement by one of several treatments. These include bone graft from the patient or donor bone from a bone bank or insertion of a metal and plastic artificial bone and joint.

Bone grafts are usually not as strong as the bone they replace. Artificial replacements (prostheses) are usually cemented into the remaining portion of bone. With time and the repeated stresses incurred during exercise, the artificial joint (prosthesis) can loosen or fracture, requiring replacement. This involves a major operation.

People who have had bone grafts or metal or plastic implants need to be very careful. They must take the advice of their orthopaedic surgeon and physiotherapist about suitable activities, so as to give the artificial part the best chance to last a long time. For example, sky-diving or hang-gliding are unsuitable sports, as are body contact sports such as football.

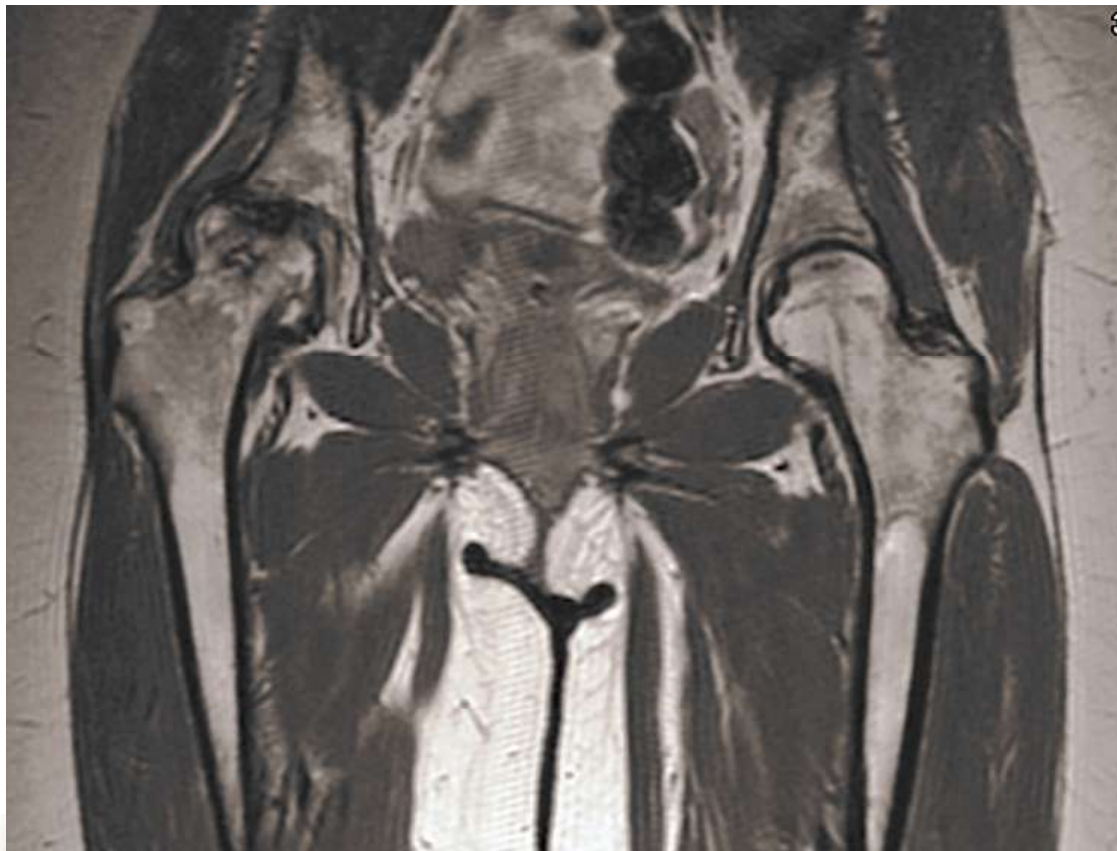
### Avascular necrosis

Avascular necrosis (AVN) is a condition where parts of long bones lose their blood supply and bone death occurs. It can be very painful. It may occur in a single bone, most commonly the hip, but can happen to other bones, such as knee, ankle, shoulder and foot bones. Bone scan or MRI will show changes, even if an X-ray is normal.

- It occurs in 10–15% of people having treatment with steroids for acute lymphoblastic leukaemia, particularly if treatment was started after the age of twelve years, but also occurs in those

undergoing bone marrow transplant. Resting the bone by avoiding weight bearing may help until healing occurs, but joint replacement is sometimes needed later in the course of this disorder.

- It can be treated with a group of drugs known as bisphosphonates. These drugs do not cure AVN but they have a major effect on improving pain and mobility in most affected people. Bisphosphonate treatment can delay and sometimes prevent collapse of an affected joint but cannot re-constitute or re-form a joint that has already collapsed. In that case, joint replacement will eventually be needed.



## Eyes

### Cancer treatment and the eye

The effects of cancer treatment on the eye will vary according to the type of tumour treated, the age at the time of treatment, where in the eye or eye socket the tumour was located, the type of treatment used and the time that has elapsed since treatment.

The tissues of the eye are generally not damaged by the use of chemotherapy, but prolonged use of steroids may affect the lens (see below).

Some tumours of the eye or around the area of the eye are treated with surgery. The long term effects of surgery depend on how much treatment has been necessary.

### Radiation and the eye

Radiation to the eye, to the areas surrounding the eye and total body irradiation (TBI) can all cause a variety of long-term effects to the eyes.

- Radiation to the lacrimal or tear glands can cause loss of tear production; this causes dry, 'gritty' eyes. Artificial tear drops can be helpful. Dry eyes are more susceptible to infection. If redness and soreness develops, it should be checked and treated promptly.
- A cataract can form after radiation to the eye, even in a young child. It is a 'clouding' of the lens of the eye and can cause blurring of the vision. This usually occurs very slowly over years. If it becomes severe enough to affect vision, the lens can be successfully replaced. The risk of cataract increases if the dose of radiation

was more than 15 Gy. Individuals who are at risk of cataracts forming are those who have had treatment with Busulphan, high dose corticosteroids and radiation including total body irradiation (TBI). Cataracts can form after either oral steroid use or topical steroid eye drops. It is important to note however that in a recent study of survivors of acute lymphoblastic leukaemia, the risk of cataract was approximately 5%, and that there was no significant impact on quality of life. The main factor for developing cataract was radiation.

- The eye may be sensitive to light (photophobia). If light sensitivity is a problem, dark glasses will reduce the glare. Sunglasses should be worn in bright light to protect the eyes and reduce the risk of cataract formation.

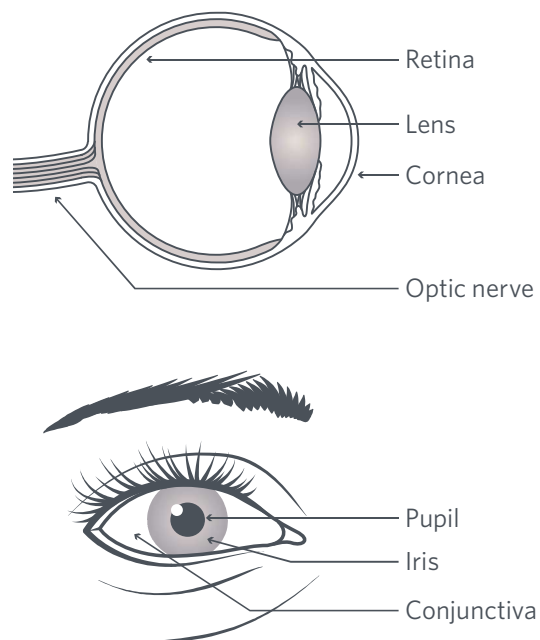


FIGURE 4. The main parts of the eye.



- Glaucoma, an increase in pressure in the eye is a rare but known side effect of the use of taxanes such as docetaxel or paclitaxel. This condition can be treated with medications, laser therapy or surgery but needs to be monitored by a specialist eye doctor (ophthalmologist).
- High doses of radiation to the retina of the eye can eventually lead to deterioration in vision. This is different from a cataract, as the retina cannot be replaced.

All those who are at high risk (radiation above 15 Gy after bone marrow transplant and individuals who have graft versus host disease (GVHD) should have a yearly review by a specialist eye doctor (ophthalmologist). All others who have had cancer treatment especially those treated for acute

lymphoblastic leukaemia should have one eye review five years after treatment has been completed, for screening purposes.

### Recommended screening and follow-up

When the eye itself or structures around the eye have received radiation, a regular check of the eyes and vision is recommended.

## Ears

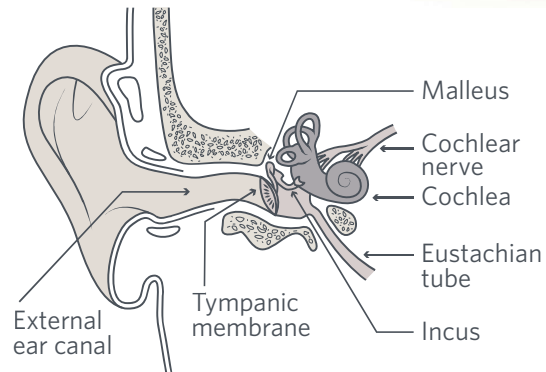
### Cancer treatment and the ears

Normal hearing depends on:

- Sound waves being able to travel to the ear drum
- An intact ear drum with air being present in the middle ear
- Normal structure of the inner ear
- Adequate function of the nerves that carry messages from the inner ear to the brain.

The platinum drug compounds (CIS-Platinum and Carboplatin) can cause damage to the auditory (cochlear) nerve. The effect is dependent on the total dose used and generally affects the very high tones, which are not important for normal speech. Hearing is generally monitored regularly during treatment and if possible the drug is stopped before hearing loss falls into the speech range. Sometimes however, despite precautions, the tones used in normal speech are affected. This is called high tone nerve deafness. Complete deafness is very rare, and only occurs with one type of chemotherapy (the antibiotic aminoglycosides such as gentamicin, tobramycin).

High doses of local radiation to the area of the inner ear, for example when treating tumours of the bones at the base of the skull or brain tumours in the back part of the brain or head (posterior fossa), can cause hearing loss, particularly in the high frequency range. This does not usually cause difficulties



**FIGURE 5.** The outer, middle and inner parts of the ear

with hearing normal speech, but may be a problem in certain situations where high frequency sounds occur, such as a noisy classroom or where there is ongoing background noise.

Radiation that has been given through the outer ear canal and middle ear can cause thickening of the ear secretions. Wax drops can be used to thin wax if problems arise with middle ear secretions and recurrent middle ear infections. Sometimes grommets, a type of small ear drain tube may be useful, if there is fluid in the middle ear. Nasal decongestants have not been found to be useful for this problem. Surgery may be helpful if thickening of the ear drum has caused hearing loss (tympanosclerosis).

When chemotherapy drugs such as Cisplatin are used as well as radiation, the risk of hearing loss is much greater. Cisplatin can damage the auditory nerve. The effect is dependent on the total dose used and generally affects the very high tones, which are not important for normal speech. Hearing is generally monitored regularly during treatment and if possible

the drug dose is reduced, or may be stopped altogether before hearing loss falls into the speech range. Sometimes however, despite precautions the tones used in normal speech are affected. This is called nerve deafness. One of the less commonly used antibiotics, Gentamicin (and Tobramycin) may also cause nerve deafness. The more commonly used antibiotic Amikacin also has a risk of hearing loss, although it is approximately half that seen with the other drugs. All are rare.

This form of deafness is not reversible, nor does mild deafness get worse after treatment finishes. A hearing aid may help with mild to moderate hearing loss but is less effective in improving severe loss.

High doses of local radiation to the area of the inner ear, for example when treating tumours of the bones at the base of the skull or brain tumours in the back part of the brain or head (posterior fossa), can cause hearing loss, particularly in the high frequency range.

### Recommendations for screening and follow-up

- Avoidance of loud noises that might worsen hearing loss (such as headphones and loud concerts)
- Preferential seating in the classroom towards the front of the class. In severe high tone hearing loss, a hearing test will be recommended; many classrooms can have a special radio-frequency microphone tuned to the hearing aid for the teacher to use.

## Teeth

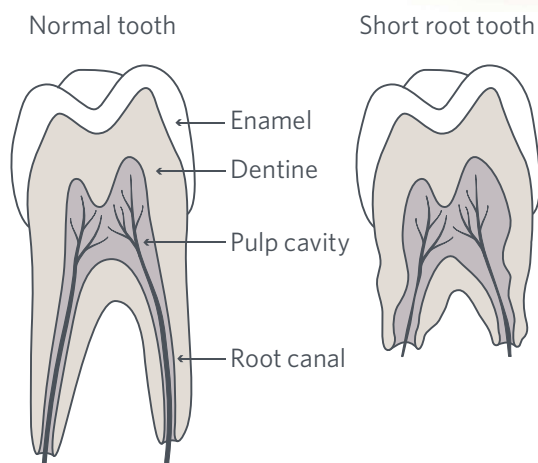
### Cancer treatment and the teeth

Chemotherapy drugs can affect the teeth. If a very young child undergoes treatment with chemotherapy, problems can occur due to the enamel or outer coating of the teeth not developing properly. Tooth decay is more likely to occur because the protective hard surface of the teeth is thinner than usual and more prone to damage by bacteria.

Radiation to the head and neck area can damage tooth buds that are in the radiation field, so that they fail to grow adequately. The roots of the second (adult) teeth are shorter than usual, can be quite an odd shape, and are not held as firmly as usual into the bone of the jaw. This means that they can become loose and may even need to be removed by the dentist.

Saliva normally protects the teeth. When it is absent or decreased, teeth deteriorate more rapidly than would normally occur. If salivary glands receive radiation, production of saliva can be decreased or lost, leading to a permanently dry mouth.

Radiation to the head and neck area can damage tooth buds that are in the radiation field, so that they fail to grow adequately.



**FIGURE 6.** A normal tooth (left) and a tooth that has been affected by radiotherapy (right)

### Recommendations for screening

- Regular yearly review by a dentist who may be able to help with these problems. The dentist should be made aware that cancer treatment has been used in the past.
- Sometimes specialist dentistry may be required for people who have mouth and teeth problems after cancer treatment.

### Thyroid gland

#### Cancer treatment and the thyroid gland

The thyroid gland is situated in the lower front part of the neck. If the pituitary gland fails to produce enough thyroid stimulating hormone (TSH) (ie. after radiation to the brain or after a tumour in the region of the pituitary), a reduced amount of this message will go to the thyroid gland and the levels of thyroid hormones will fall. This type of problem has been discussed in more detail in the chapter concerning pituitary hormones, pages 17-19.

The thyroid gland itself is very sensitive to the effects of radiation treatment but not to chemotherapy. Damage by radiation can affect its ability to respond to the TSH signal from the pituitary gland.

Underactivity of the gland (hypothyroidism) can typically occur at some time over the next five to twenty years after radiation treatment has been completed. If untreated, poor thyroid function results in slowing of growth during childhood, leading to short stature. A person with an under-active thyroid gland may have symptoms including cold intolerance, tiredness, constipation and weight gain but these are unusual.

Thyroid hormone deficiency, whether caused by damage to the pituitary gland or the thyroid gland itself, is easily diagnosed by a blood test and corrected by taking a replacement hormone (Thyroxine) as a tablet daily. After irradiation of the thyroid and/or pituitary gland, thyroid function is monitored with a blood test yearly after

the end of growth, but more frequently in a growing child.

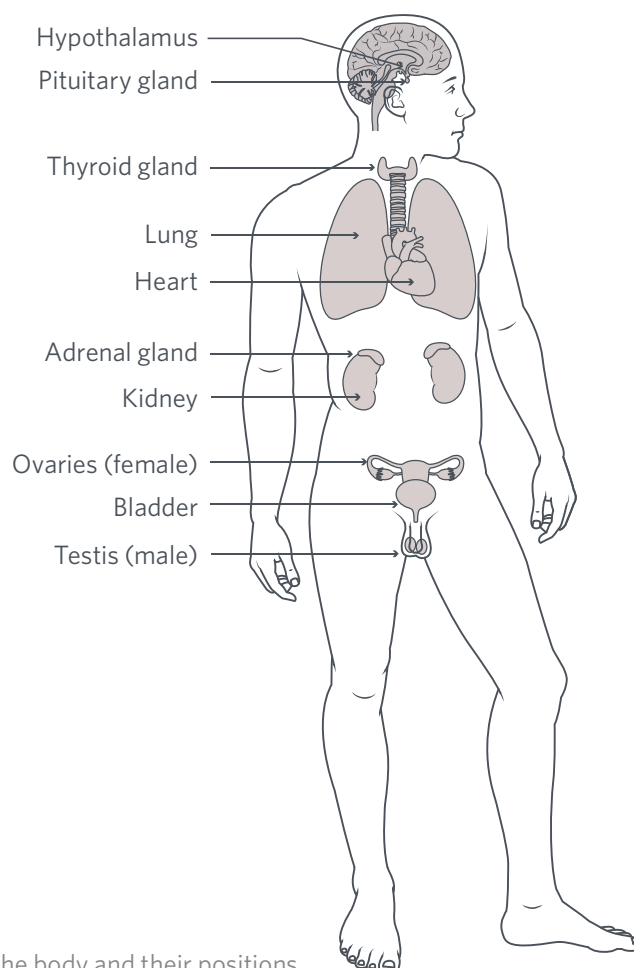
Radiation to the area of the neck can occur in several ways:

- direct radiation to the chest (such as for Hodgkin's disease and other forms of lymphoma); in children, this form of treatment is now very uncommon, and reserved for special circumstances.
- as part of total body irradiation (TBI) before bone marrow transplant.
- by scatter 'beams' at the time of local or whole brain radiation.

The thyroid gland is very sensitive to radiation and often develops lumps (nodules) after radiation exposure. The lumps may be either solid or fluid filled (cystic).

The risk for thyroid cancer after radiation treatment is approximately twenty times the usual population risk, so long term follow-up is very important.

It is now advised that an ultrasound examination be conducted every one to two years, from about two years after the original radiation treatment. This will show the structure of the thyroid gland. If any lump or nodule is identified, a biopsy can



**FIGURE 7.** Organs of the body and their positions

be easily obtained by inserting a fine needle into the lump. This test is usually performed if a lump is more than 4–5 mm in size. Cells obtained in this way can be looked at under the microscope. This investigation will give a very good idea as to whether the lump is benign or cancerous.

If there is any doubt, the doctor may advise the whole thyroid gland be surgically removed. If surgery is required it is best to remove the entire thyroid gland because the whole gland has been irradiated and more

lumps are likely to occur with the passage of time. If thyroid cancer is found at surgery, follow-up treatment with radioactive iodine may be needed. Long term surveillance should then be performed at least once per year. If a lump has been detected in the thyroid gland or removed, lifelong treatment with thyroid hormone replacement will be needed (Thyroxine).

Thyroid hormone tablets completely replace the function of the gland. There are no side effects or allergies with this treatment.

## CANCER TREATMENT AND OTHER ORGANS IN THE BODY

### Heart

#### Cancer treatment and the heart

A group of chemotherapy drugs called anthracyclines are the most likely cause of heart problems following cancer treatment in young people. The most common of these are the drugs Doxorubicin and Daunorubicin.

It is estimated that around 60% of all childhood cancer survivors will have been treated with one or more anthracyclines. These drugs are used in treating many different cancers. These compounds are very good anticancer drugs and are used against solid tumours and different types of leukaemia, but unfortunately they may also damage heart muscle. This damage may reduce the heart's pumping efficiency at some time in the future. The risk of developing problems severe enough to produce symptoms increases if high total cumulative doses are used.

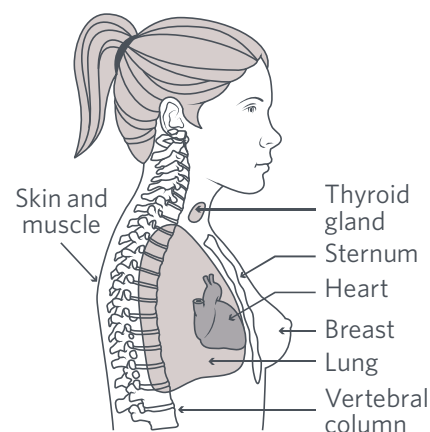
Radiation treatment to only a small part of the heart or where only small doses of radiation are received by that area, rarely causes problems. However, if large doses have been used, damage can occur to the heart muscle and the lining of the blood vessels within the heart. Radiation to any part of the body including the heart causes narrowing and changes in development of blood vessels. This can increase risks for later adult onset of arteriosclerosis or atherosclerosis and poor blood supply to the heart, with increased lifetime risks for heart attacks. Many years later this can lead to chest pain, irregular heart beat or shortness of breath with exercise.

In situations where anthracyclines and radiation to the heart have both been necessary as part of cancer treatment, the risk of heart damage is much greater.

Very young children are at greater risk of late heart problems after chemotherapy and radiotherapy. This is because their hearts are smaller at the time of treatment and need to grow substantially to meet the demands of an adult body.

Intensive exercise programs such as extreme long-distance running, and particularly weight-lifting and body-building can put extra stress to the heart. Normal aerobic exercise is safe and is encouraged. Participation in sports, team activities, walking, etc are all also encouraged.

Pregnancy and labour are also very stressful to the heart. During pregnancy, regular echocardiograms should be performed and special monitoring during labour is usually required. A caesarean section may be advised to reduce stress on the heart.



**FIGURE 8.** Side view of a chest to show the position of the different organs and why they may be damaged during radiation treatment which travels through the chest from the front or back

## Recommendations for screening and follow-up

- A cardiologist referral will be made if there are symptoms or signs of heart problems, or if the echocardiogram test shows a decrease in normal heart function.
- An echocardiogram looks at how well the heart muscle is working. It is used to show whether the heart is pumping less efficiently than normal. It is recommended that an echocardiogram be done for all individuals who have received any anthracycline drug at the end of therapy and at entry into a long term follow-up program.
- MRI of the heart may sometimes be suggested by a cardiologist to look further at heart structure and function, for Individuals who have had anthracyclines and/or radiotherapy to the chest.
- Any individuals who become pregnant and have received Doxorubicin, Daunorubicin or any other anthracycline should let their obstetrician know about their previous treatment. This is because pregnancy can put an extra strain on the heart.
- Monitoring to help reduce problems associated with early atherosclerosis and small blood vessels in the heart, is important. This includes annual tests for cholesterol and triglycerides (other fats).
- A healthy diet should be followed with low saturated fats as prescribed by The National Heart Foundation.
- Smoking should be strongly discouraged.

If a person has had radiation treatment to an area of the heart, and/or anthracycline treatment, assessment of the heart and advice by a specialist cardiologist should be sought before undertaking an intensive exercise program or commencing a pregnancy.

### Breasts

#### Cancer treatment and the breasts

Breast tissue can be damaged by radiation. The degree of damage will depend on the age at time of radiation, the amount of breast that has been treated and the dose received.

If all of one or both breasts have been treated with radiation, breast tissue that is growing in a young girl can be damaged and the breasts may not develop to a normal adult size and shape. If the radiation has affected the milk-producing glands, it may be difficult or impossible to breastfeed.

If there has been failure of breast development, surgical reconstruction with a breast implant may be possible, provided the skin is in good condition. If a serious problem with the size or shape of the breasts is thought to be present, the advice of a specialist should be sought.

Annual breast examination at a follow-up clinic is recommended as well as performing regular self-examination of the breasts. If any lumps are felt, the doctor should be consulted.

Following radiation to the breast tissue, either directly or even with relatively small doses passing through a part of the breast (for example with spinal radiation and TBI), there is an increased risk of developing breast cancer at some future time. Current estimated breast cancer risk for 12 Gy radiation exposure (eg. TBI) is approximately the same as for people who have particular breast cancer genes.

Ultrasound and/or mammography examinations may be recommended from around age 24 if cancer treatment involving this area was given at an early age.

Chemotherapy does not damage the breast. Occasionally, for reasons which are at present unknown, the breasts of some young women who have had chemotherapy in the past become a lot larger than average. If this is causing embarrassment or discomfort, advice from a doctor should be sought and possible referral to a reconstructive surgeon or discussion can be undertaken, as it may be appropriate to consider breast-reduction surgery.

## Lungs

### Cancer treatment and the lungs

Surgery to the chest can also have an effect on the function of the lungs. In removing tumours of lungs, ribs or chest wall, part of the lung may have been taken out. Removal of a portion of one lung is generally tolerated without causing any symptoms, but, if a whole lung has been removed, exercise tolerance is likely to be reduced.

Radiation therapy to or through the lungs may lead to lung problems, depending on the amount of lung involved and the dose of radiation to the area. Effects are usually quite minor. They can be assessed with a special breathing test if necessary. About one third of individuals who have had radiation can be shown to have some lung restriction on testing but most have no symptoms.

Even low doses of radiation in very young children can cause poor growth of the chest bones (hypoplasia). This can cause later problems with lung function if the chest wall is very small.

Some chemotherapy drugs can affect the lungs. Bleomycin can cause scarring of the lungs, particularly if the lungs are exposed to high oxygen concentration. In general the risk of lung damage increases with an increase in the total cumulative dose of Bleomycin.

Other chemotherapy drugs that may have effect on the lung are Carmustine (CCNU), Lomustine (BCNU), Busulphan and Cyclophosphamide. These latter drugs are often used as conditioning chemotherapy before a bone marrow transplant.

Baseline lung function tests should be performed at the time of treatment for those who have had high doses of these drugs.

It is important for people who have received Bleomycin in the past, and who require surgery for any reason, to inform the anaesthetist of this treatment. The amount of oxygen given during anaesthetic will then be limited to safe levels.

### Recommendations for screening and follow-up

Lung function and exercise reserve can be assessed with special breathing tests.

- Avoidance of smoking is mandatory.
- Baseline lung function tests should be performed at the time of treatment for all those who have had high doses of these drugs. Follow-up lung function tests can then be used as a comparison to the baseline test.
- The seasonal influenza vaccine is recommended.

### Kidneys

#### Cancer treatment and the kidneys

The main work of the kidneys is to remove waste products from the blood. The kidneys process these products which are then removed from the body as urine. Kidneys are also involved in blood pressure control.

For treatment of a cancer, surgery is sometimes required to remove all or a part of a kidney. This usually has very little long-term effect, as one kidney can usually make up for loss of the other one and can provide perfectly normal function.

Radiation therapy to the abdomen can cause kidney damage. However, this is very rare, as the dose to the kidneys is usually deliberately limited to a dose below that which leads to long-term damage.

Chemotherapy drugs such as Cisplatin and Ifosfamide can affect kidney function.

Cisplatin can reduce the ability of the kidney to filter waste products from the blood. It can also result in the loss of some vital trace elements such as magnesium from the kidneys, although this usually resolves within six months of stopping Cisplatin. Kidney function is monitored carefully during treatment and use of the drug can usually be modified before too much damage is done. Occasionally however there is a very sudden and severe change in kidney function that does not always recover. If this happened, the oncologist will probably have arranged for follow-up by a kidney specialist.

Ifosfamide damages a different part of the kidney, resulting in the loss of too much water, alkali, glucose and some salts. This is an uncommon side effect and usually recovers, but in some patients can persist for a long time after treatment. Because of the possible extra water and salt loss, people with this condition are at risk of dehydration, particularly in hot weather, and often also need to take regular supplements of salt, calcium, phosphate and bicarbonate to maintain general health and strong bones. There may be improvement in the function of the kidneys in the first year or so after treatment has stopped, but residual problems after this time tend to be permanent. Most patients remain well, provided they take the recommended replacement treatments.

Radiation therapy to the abdomen can cause kidney damage. However, this is very rare, as the dose to the kidneys is usually deliberately limited to a dose below that which leads to long-term damage.

Most young people treated for cancer will have received many courses of antibiotics. Some of these can also affect kidney function, particularly if they have been used together with the chemotherapy drugs that also damage the kidneys.

## Recommended screening and follow-up

- In patients who have only one kidney, an annual blood pressure check and urinalysis is recommended. Blood tests to check kidney function can be done, but are not routinely recommended unless there are abnormalities detected in the urine test or blood pressure.
- For other patients who have had chemotherapy which can potentially affect kidney function – regular blood pressure measurement and occasional blood tests are done. A urine test for protein may be used.

## Bladder

### Cancer treatment and the bladder

Surgery to the bladder may be required to treat some tumours. Usually only the part of the bladder involved with tumour is removed. Removing a portion of the bladder results in a smaller bladder, which cannot hold as much urine as normal. The bladder therefore needs to be emptied more often.

Sometimes, however, in order to adequately remove the tumour it can be necessary to remove the whole bladder. In this case the ureters, which drain the urine from the kidneys will usually be joined up to a new 'reservoir' made from a piece of bowel, one end of which is brought out of the abdominal wall. Urine drains from this into a collecting bag attached to the abdomen.

In a boy, if the lower portion of the bladder or the prostate gland has been involved with tumour, the prostate gland may also be removed. Very rarely, complete removal of the prostate and bladder neck may be necessary. This usually results in impotence (as nerves in the pelvis are damaged) and fertility problems, because the passage of semen is interrupted.

There are a variety of techniques available to aid the problem of impotence. Advice from a urologist is necessary. Sperm production will still occur even if the passage of sperm out of the testes is lost. Sperm may be obtained from the testes directly, using a very fine tube and suction method. In-vitro fertilisation (IVF) techniques can then be used to fertilise eggs and produce a pregnancy.

## CANCER TREATMENT AND OTHER ORGANS IN THE BODY

Sexual function and fertility after radiation and chemotherapy are discussed in more detail on pages 65–77.

Chemotherapy may also affect the bladder. Two drugs in particular, Cyclophosphamide and Ifosfamide, are toxic to the bladder lining often causing some bleeding from the bladder during treatment. This usually settles down after the drugs have been stopped, but occasionally the bladder lining remains thin, with fragile, damaged blood vessels. It may bleed periodically. It is important that the doctor is consulted if this occurs.

If needed, a cystoscopy can be performed, to look directly at the lining of the bladder. This is performed by a specialist urologist, and involves inserting a small camera into the bladder, usually under anaesthetic.

When radiation to the lower pelvis is required, the bladder will also be irradiated. If a child was very young at the time of treatment, the bladder may remain small, with a thickened, scarred bladder wall. In an older child who has had higher dose treatment, the bladder wall may become thick and scarred, losing its ability to stretch as it fills with urine. This means it can only hold a small amount of urine and will need to be emptied more frequently than is usual. If the bladder has been irradiated and high doses of Cyclophosphamide or Ifosfamide have been given, damage to the bladder lining is more likely.

Many years after radiation exposure to the bladder, or very high dose Cyclophosphamide, there becomes a small but increased long term risk of bladder cancer. Starting eight to ten years after cancer treatment it is usual to have an annual urine test looking for malignant (cancer) cells. This should be performed with the first urine sample in the morning. This is a rare finding, but if abnormal cells are detected, a bladder examination with cystoscopy will be organised with a referral to a urologist. The risk of bladder cancer goes up if the total Cyclophosphamide dose has been  $> 20$  Gy but most patients have had much lower doses.

## Gastrointestinal tract

### Bowel

Intestinal scarring (fibrosis) is the most common complication after radiation. This can occur as long as twenty years later, with the formation of strictures or narrowing of different parts of the bowel.

An increased risk for bowel cancer is now recognized after radiation to the abdomen and/or pelvis. If there has been radiation to the abdomen such as spinal radiation, radiation for a neuroblastoma, Wilms' tumour, or pelvic tumour (sarcoma), any part of the bowel will have received a dose of radiation.

This is unfortunately unavoidable. Risks for bowel cancer rise sharply over the age of thirty-five to forty in people who have had radiation exposure to the area.

### Recommended screening and follow-up

- Annual check of bowel motion for microscopic blood after age 30.
- Colonoscopy every three to five years over age 40.

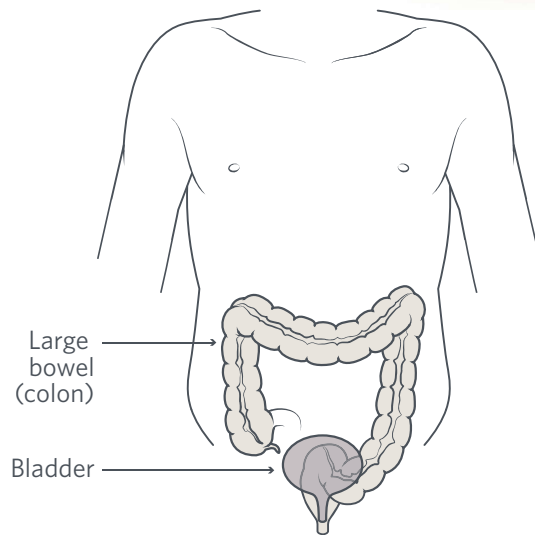


FIGURE 9. Large bowel

### Liver

Chemotherapy, particularly 6TG can cause the small veins of the liver to become scarred (veno-occlusive disease). Some individuals who have received this type of treatment who have veno-occlusive disease remain at risk for chronic liver disease especially if they have had a condition called portal hypertension. Therefore, it is important to give advice on potential toxicity of alcohol abuse, binge drinking, etc especially in teenagers and young adults.

Hepatitis B vaccination is recommended.

### Obesity and metabolic syndrome

Excess body weight is an increasing problem in the general community. This is related to a less active lifestyle in many people together with a poorly balanced diet with excess amounts of carbohydrate and fat, often from highly processed and 'takeaway' foods which often contain very high calorie content under the guise of health foods. It is increasingly recognised as a potential long-term problem in some patients after treatment for acute lymphoblastic leukaemia (ALL). It is also seen in many others who have had cancer treatment.

Risk factors of cranial radiation and corticosteroid treatment contribute, although how these contribute to obesity is not very well understood. The problem may be part due to altered hormone balance in the brain (hypothalamus) and may be particularly seen in girls who have a genetic susceptibility to weight gain. In addition a tendency to deposit fat in the abdominal area is associated with growth hormone deficiency both in children and adults.

In a recent study, when many different factors were examined, the patients who had received total body irradiation for a bone marrow transplant were at the highest risk, particularly for high levels of fats in the blood and a higher fasting blood sugar. In other studies the conclusions are that young adult survivors of childhood ALL, especially those treated with cranial irradiation, are at risk of obesity and

problems with their blood lipids (cholesterol and triglycerides) increased blood sugar, high blood pressure, and heart disease.

In groups of people who have had sudden loss of weight, very low body weight for any reason (starvation, inflammatory bowel disease, eating disorder, cancer and its treatment) the return of a normal eating pattern is frequently associated with a changed body shape, excess weight gain in the abdominal (tummy) area and high subsequent risk for metabolic syndrome (ischaemic heart disease, high cholesterol and type 2 diabetes mellitus).

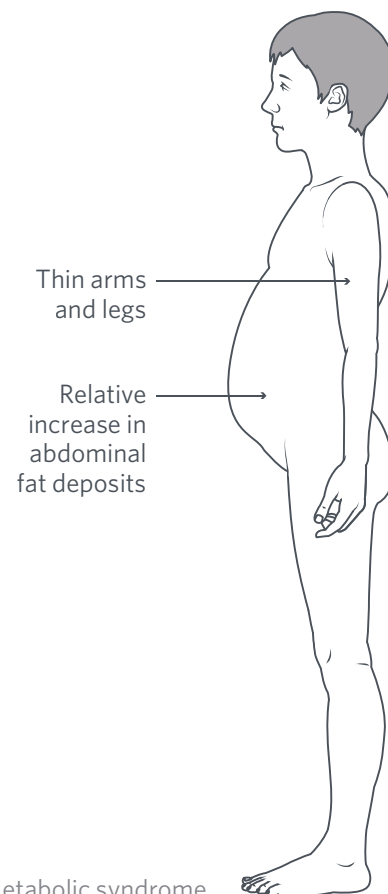


FIGURE 10. Metabolic syndrome

While to some extent this problem may be unavoidable for people who have had cancer, a healthy diet and an active lifestyle with plenty of exercise will help reduce this problem. In addition, careful attention to use of hormone replacement treatment for normal progress through puberty and maintenance of adult sex hormones will help reduce the problem further, in situations where such treatment is needed.

A healthy diet and an active lifestyle can help to reduce risks for obesity and metabolic syndrome.

### Recommendations for surveillance and follow-up

- Annual weight and body mass index (BMI) measurements help to detect early signs of a problem.
- Fasting blood sugar and lipid profile should be done every year, particularly if the individual has had total body irradiation, cranial irradiation or steroid treatment.
- Glucose tolerance testing may be recommended.





# Bone marrow transplant and stem cell transplant

## BONE MARROW TRANSPLANT AND STEM CELL TRANSPLANT

Stem cells are bone marrow cells that have the capacity to develop and change into several mature blood cell lines. Stem cell and bone marrow transplantation (BMT) offer many individuals with cancer a better chance of a cure.

A transplant may have been:

- autologous, using the patient's own marrow or blood stem cells or
- allogeneic in which the donor is either a family member, usually a brother or sister, or an unrelated volunteer from a donor registry.

Depending on the type of leukaemia or cancer treated and the age of the patient at the time of transplant, different pre-transplant conditioning therapies will have been used to:

- help to completely remove any remaining tumour
- suppress the immune system to prevent rejection of the transplanted bone marrow or blood stem cells.

BMT conditioning is normally given using a combination of chemotherapy drugs alone, with Anti-Thymocyte Globulin (ATG) to help suppress the T cells and to decrease graft-versus-host-disease, or together with total body irradiation (TBI). The radiation dose used for TBI is limited by the likelihood of long-term effects, particularly on the lungs and gastrointestinal tract. Even with very careful dose adjustments, some side effects may occur as already outlined in previous chapters.

The anti-cancer drugs most commonly used before a transplant are Busulphan and Cyclophosphamide (but additional or alternative drugs are often used). Chemotherapy before a transplant utilises much higher doses than for other cancer treatments.

Drugs and radiation effects are often additive and both can result in long-term side effects. Chronic graft versus host disease (chr-GVHD) after an allogeneic transplant, and its treatment with steroids and immunosuppressive drugs, may add to long-term effects. These effects therefore all need to be considered together.

The most common, and for many the most difficult late effects after a successful transplant are on the ovaries and testes.

These problems are discussed briefly in this section and more extensively in the following sections on cancer treatment, sexual function and fertility in both adolescents and young adults.

## Effects of BMT on Fertility

Although many chemotherapy drug regimens can cause some hormonal damage, the ones most usually associated with hormone problems are Cyclophosphamide, Melphalan and Busulphan. All these drugs have a toxic effect on germ cells (egg or sperm cells) and cause some degree of ovary or testis failure.

Long-term effects on fertility are frequently seen following total body irradiation (TBI), as both ovaries and testes are included in the radiation field.

The degree of damage and whether recovery may occur depends on:

- the primary disease for which the bone marrow transplant was being done; for example the conditioning therapy for a bone marrow transplant for relapsed leukaemia will be more intensive than the

conditioning regimen for a patient with immunodeficiency

- the drugs used to treat leukaemia/cancer before the transplant as well as those for the transplant
- whether TBI was used as part of the conditioning
- whether radiation to the brain and spine was needed in patients with leukaemia
- age at the time of treatment.

It is important to remember that fertility declines naturally with age; however, there is an increased risk of fertility being affected by being overweight, and with smoking. Therefore the same message from previous pages is reinforced; don't smoke and make sure you maintain a healthy active lifestyle.

## BONE MARROW TRANSPLANT AND STEM CELL TRANSPLANT

### Girls

Approximately 50% of girls who have had a bone marrow transplant (BMT) may start puberty spontaneously but the changes very often stop without the girl having reached adult female development and with poor growth in height.

Approximately 50% of girls do not enter puberty at all, after a bone marrow transplant, because the ovaries have been damaged and are unable to make enough female hormone (oestrogen). Female hormone replacement treatment will allow normal development to occur or to continue for those girls where progress in development has stopped.

Adolescent girls who were older at the time of transplant will experience cessation of menstrual periods after transplantation and will require hormone replacement therapy to prevent hot flushes and to have regular withdrawal bleeds (periods). Hormone therapy will also help to prevent early aging and will maintain a healthy cardiovascular system—in particular, the arteries to the heart, and good bone strength, together with reduced risks for future osteoporosis.

If chemotherapy only has been used, recovery of ovaries may occur, anytime from two to ten years after treatment. However the cumulative toxicity of chemotherapy used for the original cancer, then for pre transplant conditioning is likely to cause permanent damage.

The majority of boys and girls have severely reduced fertility after BMT conditioning, whether with chemotherapy alone or together with TBI. However, small numbers of pregnancies with the delivery of normal babies have been reported, so it is important to take precautions if pregnancy is not desired.

Reproductive technology, using donor eggs or sperm may assist in achieving a pregnancy for those who are infertile.

## Boys

If a boy having a bone marrow transplant only had chemotherapy and has never had any radiation to the testes, male hormone production will be normal after a transplant, so those boys will enter and proceed through puberty normally.

However, if radiation was used previously (eg. for leukaemia relapse in the testes) or if TBI was used as conditioning treatment prior to a bone marrow transplant, only about half of the boys will go into puberty and in many cases hormone support will be needed to complete pubertal development to adult male appearance and to obtain the best growth in height.

After radiation exposure, even if a boy went through puberty normally, hormone levels may gradually reduce as time passes and replacement treatment may be required many years after a transplant.

Boys, who had a bone marrow transplant after puberty was already completed, generally continue to have adequate testosterone secretion from the testes, provided that they were never irradiated.

## Other effects of bone marrow transplant

Bone marrow transplantation and its treatment affect a number of organs in the body:

- The thyroid gland is always irradiated when TBI is given. Thyroid tests are checked each year, as it may be many years before the function of the gland decreases. Thyroid function usually remains normal after a conditioning regimen when only chemotherapy has been used. TBI causes a significant risk for thyroid nodules (lumps) and for thyroid cancer. **Regular ultrasound is needed** (see previous chapter, page 44).
- Cataracts in the lens of the eyes occur relatively commonly after whole body radiation but are seldom severe enough to require lens replacement. **Review by an eye specialist is recommended as a screening test every three to five years or earlier if vision changes are noticed** (see page 39).
- Fibrosis and stiffening of the lungs may occur very gradually after TBI and lead to shortness of breath on exertion. Rarely, a form of chronic graft versus host disease, called bronchiolitis obliterans, may affect the lungs, causing breathing difficulty. **Following BMT, regular assessment of lung function should be performed at baseline and then every two years.** If any sudden breathing problems occur, or a cough or chest infection develops, a doctor should be consulted (see page 49).

## BONE MARROW TRANSPLANT AND STEM CELL TRANSPLANT

- Growth is often affected, particularly in children who are very young at the time of transplant. Bone growth is often decreased by TBI. When Busulphan has been used in young children, growth may be affected, even without TBI. If growth hormone deficiency also occurs, growth rate may become extremely slow.

**Regular growth measurements recorded on a growth chart will help detect problems** and alert the doctor to a need for specialist advice and management (see pages 23).

- Long term effects on the brain and pituitary gland are less common unless radiation to these areas has been part of previous treatment but it is now known that around 40% of individuals who had TBI can become GH deficient (see pages 24).
- Intermittent bleeding from the bladder may occur as a result of treatment with Cyclophosphamide either alone or in conjunction with TBI (see page 51).
- Hair re-growth sometimes fails to occur after a transplant particularly if Busulphan is given after previous radiation treatment to the head. There is no treatment that restores hair growth in this situation.  
**Purchase of a quality wig is a worthwhile investment and has an added benefit of protecting the scalp from unnecessary sun exposure.**
- Avascular necrosis (destruction of areas of bone due to reduced blood supply happens occasionally after a transplant, especially if steroids were part of treatment. This causes pain and stiffness of joints (see page 38).

## Graft versus host disease

**Chronic graft versus host disease (GVHD) may affect almost any organ except the kidneys:**

- Skin involvement may result in dryness and scarring and nails may be abnormal and cracked. Good skin care with the avoidance of harsh soaps, the regular use of non-irritant moisturisers, covering-up in the sun, and the diligent use of sunscreens, will all improve the skin. Sunburn of an area may result in a severe flare-up of GVHD in that area. **Sun avoidance in the middle of the day is important.**
- An increased chance of developing skin cancers occurs after TBI, particularly if there is also chronic GVHD of skin. This means that it is even more important to avoid direct sun exposure. Skin cancers are usually readily cured if treated early – **a doctor should be seen promptly if unusual new skin spots or changes in moles are noticed. Skin review should be undertaken annually** with photographic records ‘mole mapping’, for individuals at high risk.
- Skin cancers often occur in the scalp (basal cell carcinoma [BCC] or squamous cell cancers [SCC]) after cranial radiation or in the area of radiation exposure on the back. These can occur as early as ten to fifteen years after the original radiation treatment. Any itchy, dry patch that will not heal or disappear after a few weeks should be checked by a dermatologist for possible need for biopsy.

- Eyes may be dry and irritated. **Use of artificial tears will help.**
- The mouth is one of the most frequently affected sites for patients who may have chronic GVHD. Research tells us that oral (mouth) involvement is probably the most common location of single-site chronic GVHD. Although the overall incidence of chronic GVHD in children is lower than in adults, the extent, severity, and complications of oral chronic GVHD can also result in long term problems. Chronic GVHD can cause a dry mouth and tongue, dry lips, decreased saliva. The lining of the mouth and the top of the tongue can be thin and smooth, with patchy white areas. This can flare up and cause bad breath and taste problems. **Review by a dentist who has experience with chronic GVHD is necessary.**

Some patients develop salivary gland chronic GVHD and are at risk for developing infectious gum disease, and tooth problems. In addition to the effects on teeth, patients are at significant risk for recurrent oral candidiasis (thrush), and therefore may also need Nilstat or antifungal lozenges.

If GVHD is a problem, the doctor may advise the use of a dilute steroid mixture such as Dexamethasone, or the use of topical Tacrolimus or Cyclosporin treatment, which must be made specifically by a hospital pharmacy. If these measures don't work, the addition of other immunosuppressive treatment may be needed although this is uncommon. **Drinking water with meals**

**and chewing sugar-free gum may also help.** Artificial saliva drops can be used. Good care of the mouth and teeth is essential and **regular dentist reviews are strongly recommended.**

- For girls and women who have had a bone marrow transplant, GVHD may occur in the vagina and sometimes on the vulva, without any other signs of this problem. It can be missed if a woman is not sexually active as she may be unaware of the problem. However, if not detected and treated it can cause adhesions (sticking together) of the sides of the vagina, causing serious problems with sexual function. **Regular consultation with a gynaecologist knowledgeable about this problem is recommended.** Treatment is usually very effective.
- Chronic, severe irritation and soreness of the vulva may be due to the same problem and is sometimes diagnosed as a condition called lichen sclerosis. Specialist care is required.





# Cancer treatment and sexual function in girls

## CANCER TREATMENT AND SEXUAL FUNCTION IN GIRLS

### Effects of radiation and chemotherapy on sex hormones

This section concerns girls who have received radiation and/or chemotherapy, whether or not bone marrow transplant was used.

Radiation to the brain may impair the ability of the hypothalamus and pituitary gland to send messages to the sex hormone glands (ovaries). The ovaries themselves may also have been directly damaged by past treatments.

If brain irradiation has resulted in loss of gonadotrophins (FSH and LH), permanent female hormone replacement may be required. If total body irradiation (TBI) was given before puberty, a girl will often enter and progress through puberty normally. TBI over the age of 12 almost always results in ovary failure.

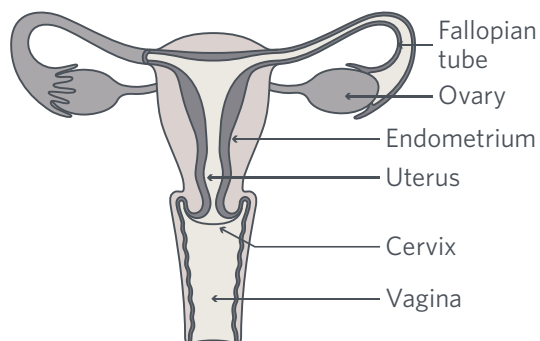


FIGURE 11. Female genital anatomy

### Effects of radiation and/or chemotherapy for girls

Cyclophosphamide is a very effective anti-cancer drug, and is used as a component of very many chemotherapy regimens. The effects on fertility are dependent on many factors, including individual dose, total cumulative dose, how frequently it is given and combination with other chemotherapy drugs.

It often causes failure of the ovaries before puberty or during puberty but many girls who have had this treatment eventually recover. Recovery may take two to ten years from the time of treatment. It is possible to have severe failure of the ovaries after treatment with Cyclophosphamide and to require hormone replacement treatment to get the girl through puberty to an adult height and with normal adult appearance. Recovery of the ovaries may take place five to ten years later.

Some women, however, who have had ovarian recovery, eventually develop an early menopause. Women who have had this type of chemotherapy are usually advised to consider having children by around age 30, if they wish to do so. This helps avoid problems of late infertility due to early menopause.

Egg (ovum) harvest is now being offered to young women who have received chemotherapy and who are likely to have an early menopause, but who do not currently have a life partner or wish for immediate conception. The technique, although potentially successful is not

without issues which are discussed in more detail on page 70.

Busulphan usually causes permanent ovary failure. Therefore, a girl who has received this drug will almost certainly need long-term hormone replacement treatment.

A woman who has had chemotherapy will have a lower number of ova (eggs) than other women. Consideration for possible pregnancy by age 30 should be given, to reduce the risk of disappointment.

## Hormone replacement treatment and sexual function for girls

If past treatment resulted in failure of the ovaries before puberty, a girl will either not enter puberty at all or will start puberty and then fail to continue to grow and develop normally. It is very important to have regular check-ups with an endocrinologist to make sure that normal growth and continuing development is taking place.

If hormone replacement treatment is required to take a girl all the way through puberty, it is given in the following way.

A very low dose of the female hormone (oestrogen) is commenced for a girl when she is about 12–13 years old. The exact timing of the start of treatment will depend on whether she is using growth hormone as well and will also depend on her particular social needs and expectations and will be discussed with each patient by her doctor.

The dose of treatment is very small to begin with and is gradually increased over 2½–3 years, to mimic the course of normal puberty. This will allow normal growth and development of a completely normal breast shape and adult body appearance. Large doses of oestrogen given too early and too fast may result in a most abnormal shaped breast, with a slightly bell or tube shaped appearance and a very large nipple. Unfortunately this shape will not alter or improve at a later time. Plastic surgery would be the only option. Slow, careful increase in oestrogen dosage will avoid this problem.

Towards the end of the three years, a synthetic form of progesterone (progestogen) is added in a cyclical fashion for two weeks at a time, so that a period occurs, as with all other girls. It is not necessary to have a period every month. Many girls prefer to take the progestogen for 14 days every second or third month, so periods are less frequent. However, it is absolutely necessary that a period does occur at least four times per year, to clean out the womb. If progestogen is not used

## CANCER TREATMENT AND SEXUAL FUNCTION IN GIRLS

regularly, in the long term the young woman will run a high risk for uterine (womb) cancer. Three month cycles of the contraceptive pill can be used as an alternative regime.

If a girl has had radiation and/or chemotherapy later in adolescence and has already completed most of her growth and development, before the effects of treatment take place, it is not necessary to go through this slow process of oestrogen increase. It may then be possible to give an adult dose of oestrogen and progestogen straight away, either in the form of the contraceptive pill or a natural oestrogen with hormone replacement treatment as described above.

These medications usually have no side effects whatsoever and should result in a normal healthy young woman with normal sexual function and a regular menstrual cycle.

However, not every girl responds to oestrogen and progestogen in the same way.

If a girl had Cyclophosphamide treatment and has been taking hormone replacement treatment (HRT), it is usually advised that she change her treatment to the contraceptive pill when she becomes sexually active. This is done on the grounds that it is not possible to be precisely sure if or when her ovaries might recover from the past effect of Cyclophosphamide and, therefore, when fertility may suddenly return. To avoid lengthy times without oestrogen, this regimen is usually taken by cutting off the lactose pills for two months of every three, and only having a period every third month. This allows the

maximum time for taking the active hormone, oestrogen, and avoids unpleasant symptoms of hot flushes, and emotional ups and downs if the ovaries have not recovered.

Side effects of nausea, headache or weight gain are common if the wrong progestogen is used. It is not possible to predict which one is correct for any particular girl. If there are side effects occurring, it is important to discuss these with your doctor, to make sure that appropriate changes are made until a satisfactory regimen can be found.

Local radiation to the pelvis may cause dryness of the vaginal skin and mucous membranes. This situation is due to a direct effect of radiotherapy and does not improve with large doses of oestrogen in excess of those normally needed for replacement treatment.

Provided the girl has adequate normal amounts of oestrogen replacement, she will almost certainly need to use extra lubricants to assist with keeping the vagina moist during sexual intercourse.

The doctor will be able to advise on the best lubricant for each patient. Normally these are very simple, with either vegetable oil or KY jelly being used.

In rare situations, if a girl has needed high dose pelvic irradiation at a young age, the vagina may be very small and not grow at puberty. Stretching or reconstructive surgery can enlarge the vagina to allow for sexual intercourse.

## Female fertility

Cranial irradiation may lead to loss of gonadotrophins (FSH and LH). A lack of these messages to the ovaries means that they are unable to respond by producing oestrogen and progesterone. Treatment is therefore needed in these circumstances, to replace the missing hormones.

It is possible to replace the missing FSH and LH when a pregnancy is desired. This treatment is very expensive and requires

daily injections. It is therefore not used as a regular daily form of replacement. This type of treatment will stimulate the ovary to produce an egg, provided the ovary has not been severely damaged by chemotherapy or radiation. Normal conception can then take place. This treatment requires the care of an IVF specialist.

Combined chemotherapy, (which includes Cyclophosphamide, Procarbazine, Busulphan) and/or local irradiation, can lead to permanent loss of ovary function and definite infertility. Potential infertility side-effects are also possible from some of the new monoclonal antibody therapies, which are just starting to emerge.

Pregnancy can be achieved if an egg from a donor (sister, friend or unidentified donor) is used, which is fertilised with the partner's sperm by means of in-vitro fertilisation (IVF). The fertilised egg is then placed in the young woman's womb. Because she cannot produce her own female hormones, however, she will need to have extra female hormone treatment to maintain the early stages of a pregnancy. Several attempts at IVF may be needed before a pregnancy is established, but once it occurs, the baby generally grows normally.

The situation can be complicated by problems within the womb itself when local radiation treatment to the pelvis has been used in the past. The womb can be stiff, with poor muscle quality and a reduced ability to stretch as the baby grows. An increased risk of miscarriage and early birth are both common problems after this type of treatment. Careful monitoring is required during such a pregnancy, with specialist care.



### Ovum (egg) salvage

After recovery from cancer treatment, families sometimes ask why eggs were not stored before treatment started. The following explanation of the issues involved may assist with understanding this difficult area.

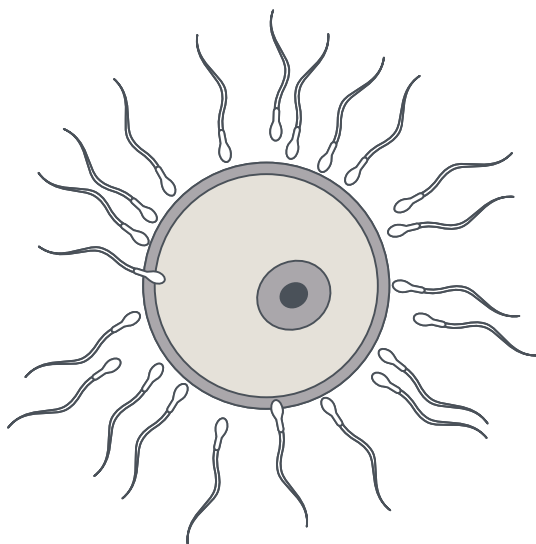
When a girl needs treatment that is likely to result in loss of fertility, both the parent and the child (or adolescent) may ask if it is possible to try and save some eggs

for the future. This can be a very difficult question to answer and needs careful thought and discussion with the doctor for the following reasons:

- Ovum salvage requires a surgical procedure to remove a surface strip of ovary, a slice of ovary or occasionally a whole ovary. In a sick child or adolescent who needs emergency care of a tumour or leukaemia, this could be a potentially dangerous or unwelcome procedure.

- At present, it is very difficult to thaw a viable unfertilised human egg. It is easy to freeze eggs, but the technology for thawing successfully is more difficult. When eggs (oocytes) are taken from a girl or woman's ovaries they need to be mature before they can be used. If the woman has a partner, the eggs can be fertilised with the partner's sperm and the embryo stored quite successfully. For younger girls, this is not an option.
- Only relatively few pregnancies have been reported anywhere in the world using stored unfertilised eggs to date. This technology is changing all the time, so the possibility of success will increase over coming years. However, there is no guarantee of success. All eggs that are taken for the purpose of storing them for some time in the future are taken on the chance that it will be possible to successfully thaw them.
- For leukaemia patients, saving these eggs may run a theoretical risk of reintroducing tumour cells at a later date.
- There are a number of unresolved ethical issues about parents choosing to take reproductive tissue from a child or adolescent who is not able to give fully informed consent. This is especially important when the tissue may be used for the purpose of possible reproduction in future, particularly if there is a possible risk to the patient in taking the tissue.

When a girl needs treatment that is likely to result in loss of fertility, both the parent and the child (or adolescent) may ask if it is possible to try and save some eggs for the future.



**FIGURE 12.** Sperm and egg





# Cancer treatment and sexual function in boys

## CANCER TREATMENT AND SEXUAL FUNCTION IN BOYS

This section concerns boys who have received radiation and/or chemotherapy, whether or not bone marrow transplant was used.

### Effects of radiation and chemotherapy on sex hormones

Radiation to the brain may impair the ability of the hypothalamus and pituitary gland to send messages to the sex hormone glands (testes). The testes themselves may also have been directly damaged by past treatments.

If the brain irradiation results in loss of gonadotrophins (FSH and LH), permanent male hormone replacement may be required.

Most of the size of an adult male testis is due to the sperm-producing cells. If there are inadequate hormone messages from the pituitary to the testes or if the testes are damaged directly, sperm production fails and the testes fail to enlarge at puberty or lose bulk in older boys.

If brain radiation has been used there may be a gradual loss of the messages (LH and FSH) from the pituitary to the testes, and the testosterone levels may decrease many years after treatment. It is important for levels of testosterone and the luteinising hormone (LH) from the pituitary gland to be monitored carefully for many years after radiation treatment, to make sure that hormone levels remains normal, or to replace hormones if they are lost.

Radiation to the testes almost always leads to complete failure of sperm production and results in infertility.

A small testis can produce plenty of testosterone but a very small testis is most unlikely to produce a normal number of sperm.

It is very common for a boy or man to have completely normal levels of male hormone after radiation but no sperm production at all.

Most of an ejaculate is made up of secretions from the prostate and other glands and is not just due to sperm. It is therefore not possible for anybody to tell whether a young man is producing sperm or not, based on the appearance or volume of the ejaculate.

Many boys and men who have had high-dose Cyclophosphamide and/or Busulphan retain their ability to make normal male hormone. However, TBI almost always leads to loss of germ cells and sperm.

TBI is also very likely to cause damage to the testosterone producing cells and hormone levels may gradually decrease and require

replacement over several years or during adolescence. In that case completion of normal puberty may require HRT.

The cells that produce male hormone may be preserved after radiation treatment, depending on the dose that was administered. They may continue to produce perfectly normal amounts of male hormone in the long term. Provided the male hormone level is normal and remains normal, there is no need for hormone replacement treatment. However radiation causes scarring to the tissue and a gradual loss of hormone function may occur over several years.

After puberty the testes are very sensitive to the effects of chemotherapy and radiation. The damage is severe after either or both treatments. If the treatment was given before the boy entered puberty, the effects of treatment might be slightly less severe, but there is always a risk of infertility and a young boy's testes are not protected from the effects of chemotherapy.

Recovery of some sperm production can occur many years after treatment, particularly if high dose Cyclophosphamide was not used during cancer treatment. As more young people survive this type of treatment into adulthood, we may see an occasional person who does continue to be fertile after treatment but at this time it is probably wise to consider infertility to be the most likely outcome.

Some boys do not like to have small testes. It is surgically possible to insert plastic testes into the scrotum if this is a major problem for an affected person. However it is necessary to think carefully about the risk of possible infection at the time of surgery and possible loss of function of testes that may be small but that produce normal amounts of testosterone. It is not wise to remove a small testis if it is producing normal amounts of testosterone because that will lead to a life-long requirement for testosterone replacement treatment. These issues need to be discussed carefully with the doctor before any major decisions are made.

### Hormone replacement treatment and sexual function

If the testes have received high dose radiation, the cells producing testosterone can be affected. If this is the case, long-term hormone replacement treatment is required for maintenance of normal sexual function, adult male appearance (both genital and general body appearance), maintenance of good skin quality, normal muscle bulk, and, particularly, normal bone quality. If hormone replacement treatment is not given where necessary, a young man may develop severe osteoporosis at a young age. The doctor will advise whether this type of treatment is necessary.

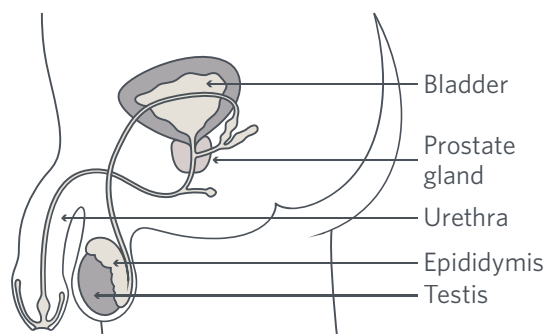
If radiation treatment to the testes was given at a young age, the affected boy is not likely to go through puberty without hormone assistance. Hormone replacement treatment is usually given from the age of around 13 years, if needed. Tablets or capsules, as a safe, synthetic male hormone, are given in small doses, increased slowly over about one to two years. Towards the later stages of puberty the treatment is changed to a stronger testosterone which is given by regular injections of a long acting male hormone which lasts eight to twelve weeks.

Adequate testosterone replacement results in normal growth and development, normal pubertal progress and a normal adult male genital appearance with adult levels of male hormone and completely normal sexual function but will not result in normal sperm production if this has been damaged by previous cancer drugs.

## Male fertility

**Male fertility is dependent on normal hormone signals from the pituitary gland reaching undamaged testes that are capable of producing normal sperm.**

Cranial irradiation results in loss of gonadotrophins (FSH and LH). These hormones can be replaced. Treatment with gonadotrophins restores the message to the normal testes so that hormone and sperm production return. However, it is too expensive to replace these missing hormones on a daily basis, so hormone replacement treatment with testosterone is usually given for day-to-day management. When fertility is required, the missing FSH can be supplied as an injection. It is usually necessary to have such treatment with synthetic FSH and LH or hCG (human chorionic gonadotrophin or LH) for somewhere between one to two years before an adequate supply of sperm can be built up within the testes, to achieve normal fertility.



**FIGURE 13.** Male genital anatomy

If the sperm-producing cells in the testes have been damaged, there is no treatment that will restore sperm production. If low numbers of sperm are present in semen, the chance of a pregnancy occurring naturally is low. It is however, possible to isolate a single sperm from a semen sample and fertilise an egg by directly injecting the sperm into the egg using techniques called ICSI (intra-cytoplasmic sperm salvage) or TESE (testicular extraction of sperm).

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The background of the page is a solid green color. Overlaid on this are several vertical stripes of a slightly lighter shade of green. Scattered across the entire green area are numerous circles of various sizes and shades of green, some appearing as if they are floating or overlapping. The text 'New treatments' is centered in the upper half of the page.

# New treatments

## NEW TREATMENTS

New drugs are becoming available every year. Although they may be very successful in treating cancer, new side effects are also being recognized so we have included a brief section here for information.

### Monoclonal antibody treatment

Our immune system is made up of many different parts. Some lymphocytes – T cells – can attack bacteria and viruses directly. Other lymphocytes–B cells–attack foreign substances in the body by making proteins called antibodies.

Antibodies attach to foreign particles and foreign proteins and once attached, they can recruit other parts of the immune system to destroy the cell to which they are attached. Many researchers have designed and manufactured antibodies in the laboratory that can target proteins on cancer cells. These antibodies are called monoclonal antibodies (M-Abs). Monoclonal means ‘all one type’ and the antibodies that are made this way are all one type against a specific target.

Each monoclonal antibody recognises one particular protein. M-Abs work in different ways depending on the protein they are targeting. M-Abs are used to treat many diseases, including some types of cancer. Different M-Abs have been made against different types of cancer–such as different leukaemias, bowel cancer and breast cancer. While these last diseases are not seen in children, more and more M-Abs are being designed against different cancers,

including paediatric cancers, and will become part of the overall treatment in combination with chemotherapy and radiation therapy in the future.

There are two main types of monoclonal antibodies, which work in different ways.

#### 1. Altering the immune system or affecting the cancer cell directly

Some monoclonal antibodies attack and kill cancer cells directly. Cancer cells are abnormal variants of a normal cell, and therefore they look like a normal cell to the immune system.

These ‘direct’ monoclonal antibodies will attach to a defined protein on the cancer cell, which then makes it easier for the cells of the immune system to find them. An example of this type of M-Ab is Rituximab (Mabthera) which is used for non-Hodgkin’s lymphoma (NHL), sometimes in Hodgkin’s lymphoma, and sometimes for other diseases such as immune thrombocytopenic purpura.

A new M-Ab, Ipilimumab, has been used for advanced melanoma and works by stimulating T-cells in the body’s immune system, and switching them on to attack the cancer cells directly.

A side effect which affects approximately 10% of patients is inflammation of the

base of the brain and a decrease in hypothalamus function and therefore pituitary function; the result is infertility which is often not recognised. However, replacement of the missing hormones FSH and LH can provide effective treatment for this problem, provided that other chemotherapy has not caused direct damage to the ovaries or testes.

Other M-Abs block the way cancer cells divide. Some cancer cells make an excess of molecules called growth-factor receptors. These molecules are on the surface of the cell, and can be stimulated by growth factors to divide. There are some M-Abs that bind to the growth factor receptor, and stop the cell from dividing. An example of this is bevacizumab (Avastin) which is used for some different types of brain cancer.

Antibodies attach to foreign particles and foreign proteins and once attached, they can recruit other parts of the immune system to destroy the cell to which they are attached.

## 2. Conjugated M-Abs; which carry a drug or radiation directly to the cancer cell

These M-Abs carry chemotherapy or radiation particles that are tagged onto them, and are designed to hook onto a cancer cell and deliver the chemotherapy or radiation directly. Examples are Gemtuzamab-used for some types of myeloid leukaemia, and Brentuximab, used in Hodgkins disease. Most of the M-Abs which are conjugated are in clinical trials and therefore are not yet part of the standard treatment but will be likely to be used more commonly in the future.

At this stage, it seems that the most common side effects seen with these drugs is at the time when they are given; eg. with fevers, headaches, nausea, chills, low blood pressure, skin rash, wheezing. However, some of these drugs can have an effect on other organs such as the kidney and liver, and as part of any long term follow-up review of someone who has received M-Abs, liver function tests, kidney function tests, and blood pressure should be checked.





# General health advice

## GENERAL HEALTH ADVICE

A healthy lifestyle is important for good health, whether or not a person has previously been treated for cancer. The following general health advice may be helpful for both avoiding illness and, where possible, for reducing the risk or impact of long term effects of childhood cancer.

There has been a tendency in the past for some young people who have had cancer, to believe that they should not be able to feel as well as other people. They might expect that they should feel 'not quite right' or a bit tired and washed out, or experience other subtle forms of ill-health. Perhaps this may be true for a few, but for most people, appropriate identification and treatment of their problems will return them to better health. A good understanding of these issues will allow proper planning for the future.

### A list of some DO's and DON'TS

#### DO

- If you are worried about ANY problem, discuss it with your doctor  
He or she is there to HELP
- Exercise regularly
- Eat a well-balanced diet
- Avoid being overweight
- Drink sensibly—alcohol should be consumed always in moderation

- Avoid sunburn (wear sunscreen, a hat and adequate clothing cover)
- Get your doctor to check your vitamin D and take a supplement if needed
- Observe any moles for change regularly. In particular if you have had radiation make sure that area of the skin that has been in the field of radiation is checked regularly by you, or your doctor if the site is on your back or in a difficult to see area
- Practice safe sex
- Ensure planned pregnancies
- Have regular pap smears
- Undertake breast self-examination and screening
- Perform testicle self-examination
- Have regular dental checks
- Seek help and support if and when you need it
- Ensure regular follow-up examinations as they are important!

## DON'T

- Smoke
- Be alone or afraid to ask for help
- Defer getting help for something that you are worried about
- Abuse drugs, including alcohol
- Ignore chronic tiredness or feeling unwell

## Cancer treatment and the risk of developing another cancer

The risk of developing a 'second cancer' is very small. It is important to remember that all people develop an increasing risk for cancer as they get older, and the risks for a person who has had a previous cancer are only slightly higher than for other members of the community.

Radiation and some chemotherapy drugs used in cancer treatment can themselves increase the risk of developing other cancers. In the case of radiation treatment these 'second cancers' occur within the treated area and may occur many years after the first treatment. Cancer occurring after chemotherapy tends to be a type of leukaemia or lymphoma. Breast cancer risk is much higher in individuals who have had chest radiation (usually TBI) and those older individuals who have had spinal radiation in the past (before 1998 in Australia) when 50% of the dose of radiation went through to the front of the chest. Regular surveillance is needed. See page 48.

Exposure to factors that are known to increase the risk of cancers should be minimised in anyone who has already survived one cancer. Smoking should be avoided and sun exposure reduced. However Vitamin D is very important for keeping bones strong. It also assists with the immune system and may help reduce future cancer risks.

Regular check-ups and a healthy lifestyle will help to maintain the best possible health. It is important to attend the doctor and the long-term effects clinic, if available in your area, to help identify any problems as they may happen. At the long term follow-up clinic visit it is important that you understand all about your past treatment and that you have a plan or 'roadmap' for good health going forward into the future.

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### General well-being and emotional issues

When children and adolescents are diagnosed with cancer or leukaemia, there is upheaval within a family for the affected person and for relatives and friends. Treatment may be long and uncomfortable and in some cases involves times of serious illness and acute danger to life. Families struggle to understand the disease and its treatment, and they fear that treatment may not be successful. When recovery or remission occurs, there is usually a great sense of relief and escape, mixed with anxiety about possible recurrence.

As young people who have had cancer grow up and become independent adults, they are often confused about the past events that took up so much of their childhood years. Some people feel a great sense of relief that everything is over and want to get on with life. Others may have a feeling of being overwhelmed by their past difficulties, the physical and emotional scars of that time and feel unable to step into the future securely. It is normal for parents of children who have had cancer to continue to worry about their child, long after he or she has grown up and become independent. This can cause frustration to the young person who wants to leave behind those anxieties.

Sometimes, the past close relationship between parent(s) and child, that was needed for support at the time of the cancer spills over to later years. The young adult may feel unable to escape from a continuation of that caring but now oppressive closeness, to the point that he or she cannot make an independent adult life.

Other children in the family may feel that they missed out on care and concern by their parents during the time their brother or sister was undergoing treatment. If these issues have not been discussed and resolved, difficulties may arise between members of the family. Professional help may be necessary to assist families during these times after treatment has been completed.

These feelings are quite natural and happen also to some families who have never had a serious illness. Nevertheless, they can be extremely frustrating and upsetting, can cause or aggravate problems at home and may be difficult to resolve. It is worthwhile speaking about these issues with the doctor. Sometimes a professional person such as a doctor or nurse specialist or social worker may be able to help.

When young people have had cancer surgery, chemotherapy and/or radiation, there may be long-term physical effects that make them feel or look different from other young people. Some people are very confident, are glad to have survived and just get on with the business of living. Others may try to make up to for 'lost' time and sometimes engage in risk-taking activities. Others find it incredibly difficult to readjust into society. They may feel that nobody

else would ever understand what they have been through, they may be embarrassed by a 'different' appearance and they may resent those feelings.

Infertility or reduced fertility is common after cancer treatment. Many young people experience great trouble in knowing when and how to address this issue with a partner-whether it should be said at once, kept as a secret, or finding just the right moment to talk about it.

### On a personal note...

Looking, feeling and being 'different' is part of growing up for everybody and is doubly difficult to young people who have had to confront a life-threatening illness and the consequences of its treatment. There is no 'best' way of dealing with these issues and no single answer that works for everybody. Friends and others you meet and need to tell of your past can sometimes be unsure of how to deal with this information. It may take them a while to digest and think about it. Don't be hurt or frightened if such important information, that has taken you so much emotion to say, is apparently received badly. Give it a while. Most people do care and will respond positively.

There are several support groups available to assist children, adolescents and young adults to feel happier and more positive about their future and with coping with past challenges of cancer and its treatment. These include a number of groups that are listed in the contacts section in the following pages.

## GENERAL HEALTH ADVICE

None of us can predict what the future holds for us. You have already had experiences that most young people never have to confront. There may still be worries and risks ahead, and your life may seem to be harder than that of all your 'normal' friends and relations. We all need to make plans in the hope that we will be alive and well to carry them out.

If you have feelings that you haven't been able to express about your treatment, your future and your relationships with family and friends, don't hesitate to talk to your doctor. There are many people who have the skills to help you and who can support you into the future.

### Further reading and contacts

Cancer Council  
615 St Kilda Road  
Melbourne, Victoria  
Telephone: **03 9514 6100**  
Helpline: **131 120**

Brain Foundation  
**brainfoundation.org.au**

The Childhood Brain Tumour Foundation  
**childhoodbraintumour.org**

Challenge  
529-535 King Street  
West Melbourne, Victoria  
Telephone: **03 9329 8474**  
**challenge.org**

Paediatric Integrated Cancer Service  
**pics.org.au**

Australian and New Zealand Childrens Haematology/Oncology Group  
**anzhog.org**

Clinical Oncology Society of Australia (COSA)  
**cosa.org.au**

The Livestrong Foundation  
**livestrong.org**

Curesearch for Children's Cancer  
**curesearch.org**

# Appendix: Treatment summary

## APPENDIX: TREATMENT SUMMARY

Ask your doctor or nurse coordinator to fill in this summary if you are unsure of your treatment methods.

**Name** .....

**Date of birth** .....

**Diagnosis** .....

### Hospital details

Name .....

Telephone .....

Clinic extension .....

Consultant 1 .....

Consultant 2 .....

Consultant 3 .....

Nurse .....

Social Worker .....

GP .....

Other numbers .....

.....

.....

## Treatment summary form

### Chemotherapy

Drugs used	Date started	Date finished
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....

### Radiotherapy

Area treated	Date started	Date finished
.....	.....	.....
.....	.....	.....

Dose .....

### Surgery

Type of operation	Date
.....	.....
.....	.....
.....	.....

### Bone marrow transplant

Donor	Date finished
.....	.....

### Conditioning regimen

TBI	Dose	Fractions
.....	.....	.....

### Chemotherapy

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## APPENDIX: TREATMENT SUMMARY

### Problems during treatment

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### Problems after treatment

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### Further treatment

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### Extra notes

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