GROWTH IMPAIRMENT FOLLOWING RADIOTHERAPY IN CHILDHOOD.

**A Thesis submitted to the
University of Edinburgh
for the Degree of
Doctor of Medicine by**

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September, 1966.

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GROWTH IMPAIRMENT FOLLOWING RADIOTHERAPY IN CHILDHOOD

It has long been known that the growth of certain tissues can be impaired by irradiation. Perthes in 1903 showed that wing development in chickens could be retarded by a dose of X-Rays. Forsterling in 1906 irradiated half the body of a rabbit and noted gross impairment of growth on the exposed side.

Unhappily, lessons learnt in the laboratory are not always remembered in the clinic. The pages of the literature and the annals of the Law Courts record many instances where irradiation of a childhood blemish has resulted in a degree of disability that could never have been matched by the untreated disease. Bisgard and Hunt (1936) and Hildebrand (1950) described bone and soft tissue deformity of children's hands following the application of radium to birthmarks which would have been far better left alone. Gregl and Weiss (1961) recount the case of a girl in whom irradiation of a haemangioma on the chest wall resulted eventually in agenesis of the breast, grossly impaired development of the muscles of arm and shoulder girdle, and shortening of the humerus: they quote eleven reports from the literature where irradiation of the nipple region in childhood, generally for some trivial condition, led to severe hypoplasia or complete absence of the breast in later life.

Such mishaps arising from the treatment of benign conditions are the result of carelessness or extreme lack of clinical judgment and should not occur. In malignant disease, however, radiotherapy can be life-saving, and it would be wrong to deny

proper treatment because of a risk of deformity.

This thesis is concerned with the growth changes in children's tissues following radiotherapy, and is based mainly on the records of those children who were treated at the Liverpool Regional Radiotherapy Centre between 1944 and 1964. Thirty-four cases who were available and appeared likely to repay further study were examined in some detail: their case histories are summarised in the Appendix.

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THE EFFECT OF RADIATION ON VARIOUS GROWING TISSUES.THEORETICAL AND EXPERIMENTAL ASPECTS.BONE.

During the nineteen thirties and forties research into the effect of radiation on the growing bone was stimulated by clinical demand. It was suggested that radiotherapy might be used to reduce the growth rate of an epiphysis stimulated to overactivity by excessive vascularity, or to retard development of normal bone in cases where such conditions as an attack of poliomyelitis threatened to produce unequal limb length (Judy, 1941, Spangler, 1941, Barr, Lingley and Gall, 1943). A more elaborate project was that of Engel (Engel, 1939) who studied the possibility of straightening a scoliosis by irradiating the convex side of the spine, correcting the deformity by producing uneven growth. Although these concepts have never found general clinical application, and probably never will, much exploratory work was done on experimental animals, and far more is known about the effect of radiation on young bone than on other developing tissues. Growing bone seems almost to invite this type of study; deviations from the normal histological appearances of the epiphysis are peculiarly clear-cut; growth impairment can be assessed with remarkable accuracy both by direct measurement and by radiology, and bears a close quantitative relationship to certain biochemical changes.

Increase in the length of a long bone is "a secondary

process of replacement and consolidation following in the wake of cartilage growth" (Stump, 1924). It is determined by changes in the hyaline cartilage of the epiphyseal plate. Flat cartilage cells in a zone near the epiphysis undergo frequent mitosis and supply larger less active cells which are impelled towards the metaphysis where they degenerate, are absorbed, and replaced by spongy bone. Normally new cell formation and cell destruction balance each other, the width of the epiphyseal plate remaining constant and the cartilage cells lying in orderly columns which do not vary in length during the period of active growth. The metaphysis is a region of great activity, cellular destruction and bone formation occurring in a zone where blood vessels and connective tissue of the marrow penetrate the epiphyseal plate and where osteoblasts and chondroblasts are found in large numbers. The newly formed spongy bone in turn undergoes transformation, being replaced eventually by compact bone.

This orderly and methodical process is remarkably easily disturbed by radiation and a dose of X-Rays too small to produce perceptible changes in the skin through which it passes may give rise to gross histological disturbance in the growing end of bone. Hinkel (Hinkel, 1943A) found evidence of damage in the distal femoral epiphysis of thirty-day-old albino rats sixty hours after a dose of 600r. The entire cartilage zone was thickened by swelling of the cells which were distorted and showed signs of nuclear damage. Their columnar orientation was deranged and the intercellular matrix was abnormally granular and increased in

quantity. In the metaphysis the degenerate cartilage cells were not absorbed as they should normally be and were imbedded in an abnormally calcified matrix, the ragged margin of which gave a frayed appearance to the edge of the epiphysis.

Osteoblasts showed signs of damage, had lost their normal orderly purposive grouping around the osteoid spicules, and were found lying free in the marrow space. The marrow cells too showed marked degenerative changes.

Seven days after irradiation the cartilage zone was wider than normal. All degenerative changes were more pronounced. Long irregular columns of damaged cartilage cells extended into the metaphysis; they were sheathed in a dense layer of mineralised matrix and were not destroyed and absorbed as they should normally have been. Metaphyseal bone was abnormal, the bony spicules being broadened and containing large quantities of mineral material. Large plaques of heavily calcified acellular matrix were prominent. The marrow cells had begun to show signs of recovery. As yet there was no apparent reduction in the growth rate.

At two weeks the width of the epiphyseal cartilage had returned to normal, although the cells remained disturbed in their appearance and arrangement. The proximal epiphyseal margin looked more ragged and irregular, and degenerate columns of cartilage cells extended still more deeply into the metaphysis. Metaphyseal new bone was very uneven in thickness and islands of obsolete cartilage cells imbedded in calcium were to be found several millimetres proximal to the epiphyseal line. At this

stage there was 1 millimetre of shortening.

At a month the outstanding changes were to be found in the metaphysis which was heavily ossified and brittle; the new bone was coarse and uneven. Measurements showed between 1 and 1.5 millimetres of stunting.

At six weeks the atypical metaphyseal bone was found to extend several millimetres farther proximal to the cartilage zone than it did two weeks earlier; irradiated femora had grown 8.4 mm. while controls had grown 10.1 mm. Growth appeared to have resumed its normal rate, but the histological appearances of the cartilage columns were to remain disturbed for a further fortnight.

The zone of abnormal ossification, which at this stage Hinkel described as the "ghost epiphyseal line", persisted a little longer, but eventually underwent remodelling, appearances being restored to normal.

The effect of dosage.

The histological changes described, accompanied by temporary retardation of growth, followed a dosage of 600r. It was shown by Bisgard and Hunt (1936) that impaired growth followed a dose of 400r to the femur of the month old rabbit while 300r produced histological changes in the femur but no retardation of growth. 100r gave rise to no microscopic damage to the epiphysis but caused alterations in adjacent bone marrow.

Doses around the 600r level produced little change in the

blood vessels supplying the epiphysis: although the number of delicate end capillaries reaching the bases of the cartilage columns appeared to be slightly reduced two weeks after radiation, individual vessels appeared normal. Larger doses, however, gave rise to very conspicuous changes. Hinkel (1943B) sacrificed young rats at varying intervals following an air dose of 950r to the lower femoral epiphysis. At a week the average calibre of the vessels was reduced and many capillaries appeared to be cut off before reaching the cartilage bone. The line of capillary tufts which normally demarcates the metaphyseal-cartilaginous junction was serrated, irregular and discontinuous. The changes became more marked over the next fortnight; the larger vessels became tortuous and the end capillaries greatly reduced in number. After a month there was some return towards normality.

Higher doses (Hinkel, 1943A) produced greater disruption: there was diapedesis of red cells and deposits of haemosiderin abounded in epiphysis and metaphysis. The diaphyseal vessels lost their normal structure and formed large thin-walled vascular lakes. These changes, which when extreme were associated with almost complete avascularity of the epiphysis, persisted for a long time and were found as long as eight months after irradiation.

Radiation then may exert two effects on the epiphysis, one direct on the cartilage cell and osteoblast, the other indirect and effective only at higher doses, mediated by interference with the vascular supply. This consideration may be of

importance when considering the effect of different levels of irradiation energy and will be referred to later.

Barr, Lingley and Gall (1943) showed that growth retardation in the femora of albino rats was proportionate to the dose delivered to the epiphysis within a range tested from 665r upwards, a point of maximum response being reached at between 1335r and 1800r, when growth ceased completely and premature epiphyseal union took place. Puppy bone appeared more resistant and growth was eventually resumed after doses of 2000r (Barnhard and Geyer, 1962). Doses within the range 800r to 1200r reduced growth of puppy femora for some fifteen weeks after which the normal rate was resumed (Reidy, Lingley, Gall and Barr, 1947). Following doses up to around 1500r epiphyseal closure took place at or slightly before the normal time, (Brooks and Hillstrom, 1933, Bisgard and Hunt, 1936).

Doses cited were delivered by single exposures to radiation. There is general agreement that fractionation markedly reduces the degree of resulting growth impairment (Shields Warren, 1943, Gall, Lingley and Hilcken, 1940, and Brooks and Hillstrom, 1933).

Radiological changes following epiphyseal irradiation.

The first change noted is the development of a sclerotic line in the metaphyseal region which doubtless corresponds to the area of abnormal mineralisation noted by Hinkel. This zone appeared within forty-eight hours of a dose of 2000r to the epiphysis of puppies, being well marked at five days and heralding complete growth arrest which was established two days later.

Following a dose of 800r the zone of increased density faded within four weeks (Barnhard, Davies and Kamp, 1963), but following 1500r it persisted unchanged for the duration of the experiment (eight weeks). If growth is resumed, this zone of increased density is carried into the shaft of the bone and has been compared to the "lines of growth arrest" described following acute disease in early childhood (Hinkel, 1943). The development of adjacent periosteal new bone is apparently retarded in proportion to epiphyseal growth (Dahl, 1934) so that the final outline of an irradiated end of bone is close to normal, except where there has been uneven mechanical strain, or one part of the epiphysis has been irradiated more heavily than the rest (Shields Warren, 1943). The effect of uneven irradiation and stress will be discussed later.

Biochemical changes following epiphyseal irradiation.

Retarded bone growth following irradiation is closely associated with local biochemical changes. Osteoblasts are responsible for the elaboration of alkaline phosphatase (le Gros Clarke, 1945) and the enzyme in turn plays an important part in the growth of bone, being necessary for true calcification. Osteoblasts are destroyed shortly after radiation and their disappearance is closely correlated with a fall in the alkaline phosphatase content of growing bone (Hinkel, 1953, Levy and Pugh, 1952). It has been shown (Woodard and Spiers, 1953) that the change in the alkaline phosphatase level of young mouse bone bears relation to the absorbed energy and degree of histo-

logical damage, falling to a minimum two or three weeks after a dose of 900r and returning to normal within some fifty days, reduction being more marked and restoration slower and less complete following higher doses. There are remarkably consistent differences between dosage and biochemical change within the range of 900r to 1500r, provided kilovoltage is kept constant. For doses of 2000r and above there is no consistent difference in the depression of phosphatase activity, suggesting that the point of maximum effect is reached at about 2000r although clinically detectable growth ceases at about 1500r. Woodard and Spiers used alkaline phosphatase assays: these, however, are elaborate and time consuming. Wilson has produced evidence that the uptake of radioactive phosphorus by the irradiated bone end indicates damage with equal precision, and has shown that assessment presents considerably less technical difficulty, (Wilson, 1956).

The effect of age on radio-sensitivity.

It is generally held that the degree of impairment of bone growth produced by the same dosage of X-Rays is greater the younger the animal (Forsterling, 1906, Recamier and Tribondeau, 1905, Moss, 1959). Hinkel (1942) showed that the minimal dose required to produce stunting of rat femora rose steadily from about 500r when the animal was one week old to around 2400r at six months. Small doses produced early histological changes in the younger but not in the older animal: recovery was rapid and complete. Large doses produced delayed but severe permanent

epiphyseal damage associated with vascular changes in the older animal, while injury following the same dosage was temporary and less severe in the younger rats. His findings suggest that the direct effect of radiation on the epiphysis is more marked at an early age, while the indirect effect bears more heavily at a later stage. Barr, Lingley and Call, (1943), found greater growth inhibition of bone in 30 day than in 90 day old rats following the same dosage, and Engel (1938), working with rabbits, confirmed their finding that growth was more readily disturbed in the younger animal. Barnhard and Geyer, (1962), however, found that retardation was more easily produced in the distal radial epiphysis of the puppy than in the more slowly growing ulnar epiphysis, and Wilson (1956) found a similar distinction between the femur and tibia of mice when the knee region was irradiated.

Sensitivity then may not be dependent on age per se, but on the degree of cellular activity at the time of irradiation, a concept which accords with generally accepted radiobiological principles.

The influence of the energy of applied radiation.

Radiation generated at 100 to 250 Kilovolts is absorbed mainly by the photo-electric process and absorption varies with the density of the material irradiated. If the density of soft tissue is regarded as 1, that of compact bone is about 1.8 and therefore bone irradiated by energies within this range will be subject to considerably higher dosage than adjacent muscle or connective tissue. The dosage to soft tissue inclusions in bone

varies inversely with the size of the cavity that contains them, but is higher than that in tissues not so enveloped (National Bureau of Standards Handbook, 78). As the energy of applied radiation increases, however, photo-electric absorption becomes less important and energy is transferred by the Compton process which is independent of the density of the absorbing material.

The rad, which is an absolute unit of energy absorption, makes allowance for differences in density of irradiated material, so that dosages are better expressed in rads than in rontgens. The table below, taken from the Handbook 87 of the National Bureau of Standards, expresses the difference in dosage to be expected from the same number of rontgens delivered at varying energy levels.

FACTORS TO CONVERT RONTGENS TO RADS

HALF VALUE LAYER (mm. Cu.)	FACTOR FOR BONE (f b)	FACTOR FOR SOFT TISSUE (f t)	RATIO fb/ft
0.75	2.2	0.95	2.3
1.0	1.9	0.95	2.0
2.7	1.3	0.96	1.35
6 - 8	1.0	0.98	1.02

The damage produced in cortical bone by radiations of various energies has been studied (Rosenthal and Marvin, 1957) and it has been shown that 6000r delivered at a H.V.L. of 0.4 mm. copper produces injury histologically indistinguishable from

that resulting from 1200 r at H.V.L. 2.4 mm. Copper.

As a great part of its blood supply approaches the epiphysis through bone one might expect medium and low voltage irradiation to produce avascularity and indirect damage more readily than X-Rays generated at higher voltages. The epiphyseal cartilage itself, however, is of approximately unit density, so that any direct damage on the cartilage cell should not be voltage dependent. (Osteoblasts, on the other hand, are situated in the metaphysis, where the density varies between that of soft tissue and that of bone.) It is tempting to postulate that the direct action of radiation, which seems to be more important at lower dose levels and in younger subjects, should be less voltage dependent than the indirect action mediated through vascular changes.

Such experimental evidence as is available is contradictory. Call, Lingley and Hilcken (1940) found little difference between radiations generated at 200 and 1000 K.V. over a wide range of dosages in their effectiveness on stunting rat femora. Arkin and Simon (1950), on the other hand, found that it required 2700r from a radon seed to produce the same degree of deformity as 1000r from 140 K.V. X-Rays (H.V.L. 0.5 mm. Cu.) on the vertebra of a goat. Woodard and Spiers (1953) showed that the depression of the alkaline phosphatase activity in growing bone was greater for 100 K.V. than for 1000 K.V. radiation by a factor of 1.35: 1.

The question is of some clinical importance and has not received the attention it deserves.

The influence of uneven irradiation and mechanical strain on the irradiated epiphysis.

If an entire epiphysis is evenly irradiated growth impairment is equal throughout its extent and the bone developed from it, although small, is of normal contour (Gratzek and others, 1945). Uneven irradiation, however, results in eventual distortion. Barnhard and Geyer (1962) showed that if a dose of 2000r was applied to part of the active epiphysis of a dog, growth stopped in the irradiated part only. If the lateral half was irradiated continued activity of the medial half gave rise to epiphyseal tilting and growth followed the direction of the tilt, leading eventually to angulation of the bone. If, on the other hand, the central part of the epiphysis was irradiated, leaving an untreated zone on either side, the direction of bone growth remained unchanged. As the bone developed a radiologically translucent well appeared, corresponding to the bone that should have developed from the damaged part of the epiphysis which deepened as the bone grew. Eventually the well was filled in by remodelling from adjacent bone, leaving a picture indistinguishable from normal.

Engel (1938) believed that epiphyseal tilting was in part due to mechanical factors and showed that an identical degree of growth restraint in the rabbit was associated with far more angular deformity in the hind than in the fore limb, which he attributed to the effect of weight-bearing. Reidy, Lingley, Gall and Barr (1947) working with dogs, also concluded that weight-bearing was responsible in part for distortion of an

irradiated limb.

It appears then that gaps in bone, resulting from partial irradiation of an epiphysis, can be repaired from adjacent bone provided they have not been obliterated by collapse, and that mechanical strain may lead to distorted bone growth following irradiation. Both these considerations may find clinical application.

CARTILAGE.

Hyaline cartilage and fibro-cartilage are relatively resistant to radiation and the cartilaginous lining of joints has frequently been reported as showing no histological change following doses sufficiently large to arrest growth of the neighbouring epiphysis. Horwitz and Dillman (1944) found no change following fractionated doses between 3000r and 8000r in year old dogs. Reidy and his colleagues (1947), however, sacrificed puppies at intervals following irradiation of the limbs and found that the articular cartilage was attenuated, of poor texture and sometimes eroded. The longer the interval between irradiation and death the more marked were these changes, and it is possible that they may have resulted not from irradiation but from abnormal mechanical strain on the joint, resulting from bone shortening and deformity. There is an obvious analogy with the tendency to osteoarthritis in a hip the mechanics of which have become distorted by a badly reduced fracture of the femur.

TEETH.

Recamier and Tribondeau (1905) exposed the antero-lateral aspect of a kitten's face to X-Rays and noted more marked retardation of development in the teeth than in the facial bones. Leist (1927) made a more detailed study in rats and found severe damage to the odontoblasts of the germinal layer, resulting in arrest of tooth growth. Repeating the experiment with puppies, he observed delayed dentition, slowed rate of growth and incomplete development of teeth, the degree of effect varying with dosage. Unfortunately details of dosage are not available although doses were "for the most part greater than those used in therapy".

SOFT TISSUE.

Impaired soft tissue growth is frequently mentioned in clinical reports, usually in association with maldevelopment of associated bone. No histological descriptions can be found, however, and no account exists in the literature of the mechanisms by which such impairment is produced. The author's theories are advanced in the clinical section where they can be more appropriately discussed than under the present heading.

THE EFFECT OF IRRADIATION ON VARIOUS GROWING TISSUES.

Clinical Considerations.

Experimental work is an orderly process: extraneous factors likely to confuse results can be excluded, subjects for study are carefully selected, and litter-mate is compared with litter-mate. The type of investigation with which we are now concerned is by contrast untidy and unmethodical. The subjects under consideration are children of varying ages and degrees of health suffering from conditions some of which may themselves affect growth. Factors such as dosage, fractionation, and kilovoltage are governed by considerations of cure and can not be varied for the purpose of the investigation, and like can rarely be compared with like. For these reasons conclusions drawn must often be tentative, but sometimes gain strength when reinforced by experimental findings.

Bone.

Histological descriptions of the irradiated epiphyses of children are few (Neuhauser and others, 1952, Spangler, 1941). There is no evidence to suggest any qualitative difference from the effects of irradiation in animals, but detailed accounts are lacking. Mechanisms of bone growth, however, vary in detail between different species - in the rat, for example, epiphyses do not normally fuse during the lifetime of the animal - and findings with experimental subjects need not necessarily apply

in clinical practice.

Moss (1959) stated "no single dose can be regarded as safe for all circumstances but doses of 400r or higher may produce clinically noticeable growth disturbance in small children". This figure is often repeated in the literature and seems to be accepted as the lowest dose likely to produce damage: it accords with experimental findings. At the other extreme of dosage there are instances like that cited by Bisgard and Hunt (1936). Their patient, a girl of six, had been treated elsewhere by radium at the age of one for a haemangioma of the index finger. The finger had ceased to grow and the epiphyses of the distal phalanges had fused; the soft tissue was atrophic and the skin grossly telangiectatic. Dosage was uncertain, but a similar degree of damage was observed by Hildebrand (1950) in the hand of a child who had been treated at the age of seven. A calculated dosage of 4800r to the skin and 2000r to the epiphyses had been delivered over a period of a few days.

The present paper is concerned with the effect of dosages between these extremes: most cases have been treated along orthodox lines and to conventional dose levels for malignancy. There has been no opportunity to study the effect on growth of the very high doses currently given in the treatment of osteogenic sarcoma of the limbs.

The long bones are usually selected for the experimental study of the effect of irradiation on growing bone as impairment can be seen in its most uncomplicated form and measured with accuracy. In children, however, the limbs are usually

irradiated for some condition which may itself impair the growth of bone: for this reason it has been impossible to include a number of cases of bone tumour and dysplasia in our series, and only seven cases were thought to merit detailed study (Cases 1 - 7: Table 1.). Findings have been reinforced by consideration of ten patients in whom the abdomen was irradiated (Table 2.). The treatment of some intra-abdominal tumours in children necessitates irradiation of large volumes of normal tissue which include vertebrae and ilium. Although subsequent growth impairment can be confidently ascribed to the effect of X-Rays, changes in these irregular bones can not be directly measured and can only be graded approximately according to their degree of severity. An additional difficulty in assessment arises if the whole abdomen has been treated and no normal bone is available to act as a control.

The cases studied were treated over varying periods of time. In an attempt to introduce uniformity, the single dose calculated to produce the same effect as the fractionated series has in each case, in Tables 1 and 2, been estimated by Fowler 's method. (Fowler 1965: Formula A, based on clinical data and animal experiments.). The doses so obtained are probably on the high side but serve for purposes of comparison between cases.

No growth impairment has been observed following irradiation of the shaft of long bones provided epiphyses were spared. The tibial shaft of Case No.3. was irradiated when the patient was seven. (4 MeV: 4500 rads: 23 fractions: equivalent single

TABLE NO.1.

DEGREE OF GROWTH DISTURBANCE FOLLOWING IRRADIATION INVOLVING LIMBS.

Case		Age		Dose to bone		Field size		Voltage		Number of fractions	Dose adjusted to single fraction*	Degree of developmental impairment	
No.	Treated	Assessed	Epiphysis	Shaft	(cm)							Bone	Soft tissue
1.	5	12	4000 rads	4000 rads	24 x 6	4 MeV	15	1500 rads				6 cm. shortening femur. Osteoporosis. Early fusion of epiphysis.	Marked. 5 cm. difference in mid-thigh girth.
2.	6	28	2600r	2600r	15 x 10	230 KV	8	1200r				6 cm. shortening humerus. Slender bone. Osteoporosis. Altered trabeculation. Marked impairment scapula, clavicle. (Fig.1.)	Marked. Breast, subcutaneous tissue, muscle. (Fig.13.)
3.	7	13	nil	4500 rads	20 x 7	4 MeV	17 (irreg.)	1700 rads				No change in irradiated tibia.	Marked. 8 cm. difference in calf girth.
4.	8	15	4500 rads	4500 rads	12 x 7	4 MeV	16	1700 rads				No apparent effect on irradiated humerus.	Negligible soft tissue impairment.
5.	12	16	nil	4500 rads	14 x 10	4 MeV	20	1650 rads				No apparent effect on irradiated humerus.	Slightly impaired muscular development of arm.
6.	13	25	2000r	3000r	35 x 10	230 KV	15 shaft 10 epi-physis	1200r shaft 900r epiphysis				Slight. 1.5 cm. shortening of femur.	Moderate impairment fat and muscle: 6 cm. difference in thigh girth.
7.	15	19	4400 rads	4400 rads	21 x 13	4 MeV	16	1700 rads				Slight: 2 cm. shortening of humerus.	Moderate impairment muscle and subcutaneous tissue of shoulder girdle.

* See Page 12 for method of calculation.

TABLE NO.2.

DEGREE OF GROWTH DISTURBANCE FOLLOWING IRRADIATION OF ABDOMEN

Case No.	Age		Field size (cm)	Proportion of abdomen irradiated	Voltage	Dose	No. of fractions	Dose adjusted to equivalent single fraction *	Degree of developmental impairment.	
	Treated	Assessed							Bone	Soft tissue
8.	6 mths.	13 yrs.	a) 15 x 10 b) 10 x 8	a) half + b) tumour area only	230 KV	a) 1800/1700r b) 5000/4000r	a) 15 b) 30	a) 700 r b) 1450 r	Marked: ilium, vertebrae, rib, femoral head. Slight scoliosis.	Marked: abdominal and lumbar muscles. Slight: buttock.
9.	19 mths.	7 yrs.	15 x 10	Half +	230 KV	3500/3000r	30	1050	Marked: ilium, vertebrae, ribs. Slight scoliosis.	Marked: abdominal and lumbar muscles and buttock.
10.	2½ yrs.	20 yrs.	a) 20 x 20 b) 10 x 8	a) whole b) half	230 KV	a) 1000/ 900r b) 2500/2250r	a) 10 b) 30	a) 400r b) 750r	Moderate: ilium, vertebrae, ribs.	Moderate: abdominal and lumbar muscles. Slight: buttock. Marked: abdominal fat.
11.	2½ yrs.	9 yrs.	15 x 12 Chest also treated.	Half +	230 KV	3000/2500r	30	900r	Slight: ilium, vertebrae.	Moderate: abdominal and lumbar muscles. Slight: buttock.
12.	3 yrs.	10 yrs.	15 x 10	Half +	230 KV	2800/2800r	20	1000r	Slight: ilium, vertebrae.	Moderate: lumbar and abdominal muscles. Slight: buttock.
13.	3 yrs.	9 yrs.	12 x 10	Half +	230 KV	3700/3500r	30	1200r	Moderate: ribs, ilium, vertebrae.	Not assessed.
14.	6 yrs.	17 yrs.	15 x 12 Chest also treated.	Half +	230 KV	3500/3450r	30	1150r	Moderate: ilium, slight lumbar scoliosis. Slight: rib, vertebrae. Premature fusion of irradiated iliac crest.	Marked: abdominal and paraspinal muscles. Marked: abdominal and thoracic fat. (Fig.11.)
15.	8 yrs.	20 yrs.	20 x 15	Whole	230 KV	3000/3000r	30	1000r	Slight: shortening of iliac crests.	Slight: narrowing of trunk.
16.	11 yrs.	14 yrs.	33 x 22	Whole	4 MeV	3000/3000 rads	20	1100 rads	Nil	Nil
17.	12 yrs.	26 yrs.	15 x 12	Half +	230 KV	4300/4000r	20	1500r * See Page 12 for method of calculation.	Slight: vertebrae, ilium.	Marked: abdominal fat. Slight: abdominal and lumbar muscles.

Right

Fig.1.

Left

Markedly impaired growth of left humerus in a patient who had been treated by X-Rays at the age of six for enlarged axillary glands. (Case No. 2.)

fraction 2100 rads). Films taken seven years later showed no growth restriction in length or width of bone. In Case No. 5. the humeral shaft was treated to a similar dosage when the patient was twelve: the bone showed no growth disturbance four years later. Both these cases did, however, show gross attenuation of soft tissue. Bisgard and Hunt (1936) showed that growing rabbit bone was not affected by a single fraction of 1500r provided the epiphysis was spared: it appears that the shaft of the human bone is also relatively resistant and that periosteal new bone formation is less readily affected than epiphyseal growth which, it will be shown, is very sensitive to doses of the level administered.

Impaired bone growth in younger children treated by conventional therapeutic doses can be severe. Case No.1. was treated at the age of five (4 MeV: 4000 rads: 16 fractions: equivalent single fraction 2200 rads). The whole femur, which was involved by an eosinophilic granuloma, was irradiated. X-Rays taken seven years later showed six centimetres of bony shortening. The head and neck of the bone were small and there was premature epiphyseal union.

Case No. 2. forms an interesting comparison to Case No.7. Both were treated for enlarged axillary glands, No.2. at the age of six and No. 7. at the age of fifteen. Equivalent single fraction in Case No.2. was 1200r of 230 KV radiation and in Case No. 7. 1750 rads at 4 MeV. Both were re-examined in early adult life: X-Rays of the humerus in Case No. 2. showed osteoporosis of the treated end with 6 centimetres of shortening and

Fig. 2.

Marked impairment of bone growth following irradiation at the age of six months
for nephroblastoma. (Case No.8.)

impaired development in width: scapula and clavicle were also small (Fig.1.). The bone in Case No. 7. showed about 1 centimetre of shortening and was normal in width. Case No. 4. showed no growth disturbance at the age of seventeen - seven years after megavoltage irradiation by equivalent single fraction of 1000 rads to the upper end of the humerus. Case No. 6. who was treated at the age of thirteen by 230 KV X-Rays to the whole femur (equivalent single fraction 1200r to the epiphyses) showed barely detectable bone shortening at the age of twenty-three.

Of the ten children treated by abdominal irradiation, two (Nos. 8 and 9) treated at the ages of six months and eighteen months, showed marked growth impairment of bone, (Fig. 2.): dosage in No. 8., however, was unusually high. Three cases treated at the age of eight and over showed little or no disturbance of bone development. The remaining five, whose ages were intermediate, showed changes of slight to moderate degree which did not vary consistently with age.

Examination of Tables 1 and 2 leaves little doubt that the effect of radiation on bone growth is more severe in the younger than in the older child.

Too few cases were treated by megavoltage to allow comparison between the effects of irradiation of higher and lower energies. In only four (Cases No.1,4,7 and 16) could one have expected demonstrable impairment of bone growth. It may not be significant that Cases No.4 and 16 were the only comparable subjects showing no bone change, and that in Case No.

Fig. 3.

Characteristic bone pattern following irradiation to right half of abdomen in childhood. Under-development of ilium and lower ribs: slight wedging of vertebrae. (Case No.10.)

Fig. 4.

Unilateral "wasp-waisting" following radiotherapy to right half of abdomen in childhood. (Case No.10.)

7 changes were slight. A more profitable assessment can be made by comparing the findings in different series of cases submitted to abdominal irradiation, usually for nephroblastoma. The Liverpool cases were mainly treated by radiation of half value layer around 2.8 millimetres of copper: a London series was treated by rays of H.V.L. 2.5 and 10.0 mm. Cu. (Williams, 1964). By contrast the authors of three American series employed radiation of much lower energy (0.9 to 1.5 mm.Cu.) (Neuhauser and others (1952), Vaeth and others (1962), and Rubin and other (1962)). The fields applied in the treatment of nephroblastoma commonly extend from diaphragm to iliac fossa and reach from flank to a variable distance across midline. The resulting change in bone and soft tissue pattern is quite characteristic: the irradiated lower ribs are short and the ilium underdeveloped: the soft tissues, which are less bulky than normal, follow the abnormal outline of the skeleton, giving the appearance of one-sided wasp-waisting (Figs. 3 and 4). Growth impairment in the vertebrae when symmetrical is impossible to detect: uneven irradiation, however, leads to uneven growth and, due perhaps to penumbra or to day to day differences in setting-up, the vertebrae do not always appear to be irradiated to the same dosage throughout, even when treatment has been planned to include the whole width of the spine. Many of the Liverpool cases showed wedging of the vertebrae, narrow to the more heavily irradiated side, associated with a small pedicle and transverse process (Fig.5.): trabeculation, however, was never disturbed and alterations in contour were never gross.

Fig. 5.

Vertebral wedging following irradiation to the right side of the abdomen, compensated by enlargement of the right side of the inter-vertebral discs. (Case No. 10.)

Williams, who may have employed wider fields, found no changes whatever. By contrast, Neuhauser, reviewing a series of thirty-four cases of nephroblastoma treated by a bewildering assortment of doses and fractionations, found that vertebral bodies receiving over 1000r showed a dense line parallel to the epiphyseal plate, giving in extreme cases the appearance of a "bone within a bone", while doses over 2000r produced changes in vertebral growth irrespective of the age of the child.

Heavier irradiation produced gross irregularity of the epiphyseal plate, while doses at the upper level of therapeutic tolerance gave rise to extreme irregularities of the vertebral body. A number of these heavily irradiated children developed cartilaginous exostoses of ribs and ilium. Vaeth found marked contour changes in many of his thirty cases, and Rubin, Duthie and Young also confirmed Neuhauser's observations. They found that damage, which they could not relate to the age of the patient, became apparent six months after heavy doses and a year after lighter irradiation.

The American cases appear to have been treated less systematically and fractionation and dosage factors were not the same as in the Liverpool and London series. All series, however, were similarly composed mainly of cases treated at levels of dosage approaching the limit of therapeutic tolerance and it seems reasonable to attribute the marked difference in the effects observed to the different energies of the radiation employed.

Our series provides little evidence of the effect of

Fig. 6.

Premature fusion of epiphysis for irradiated right iliac crest. (Case No. 14.)

irradiation on the time of appearance and fusion of the epiphyses. Premature fusion was seen in Case No.1. where the centres for the upper end of the femur had joined at the age of thirteen following treatment seven years earlier and in Case No. 14, where the epiphysis for the iliac crest, irradiated when the child was six, was not in evidence when she was seventeen (Fig.6.). Case No.8. was irradiated at the age of six months: the centres for the femoral head and greater trochanter had appeared but were small when he was eleven, while that for the lesser trochanter was absent although it was present on the un-irradiated side. It would be rash to suggest, on the evidence of this single case, that radiation can cause the non-appearance of an epiphysis: it is, however, well established that radiation can lead to early union.

Different bones may vary in their degree of sensitivity. We found no evidence of retarded growth in the calvaria of six children (Cases Nos. 29 to 34) examined at varying intervals after irradiation for brain tumours. The jaws, however, appear to be relatively sensitive. Case No.18. was treated as a two-month-old baby by two fractions separated by a week, dosage to the left side of the jaws being in the region of 850r. When the child was seven the mandible and maxilla were smaller on the treated side, irradiated teeth were all small and their eruption had been retarded (Fig.7.). In two cases (Nos. 23 and 24) radiotherapy to neck and mediastinum had been applied by the "bridge" technique involving symmetrical irradiation to the jaws: the appearance of these patients seen separately would have

Fig. 7.
Under-development of left mandible and maxilla following irradiation: the teeth on the left side were small. (Case No.18.)

Fig. 8.

Characteristic appearances following irradiation to neck and lower half of face in childhood. Note the tapering chin and narrow neck.
(Case No. 24.)

passed for an extreme of normal, but when they were examined together the shape of the jaws, tapering from the zygoma to a narrow pointed chin, was so similar that it was felt it must have been conditioned by treatment rather than by nature (Fig.8.).

Joints.

Widening of the pubic symphysis and the sacro-iliac joint was noted in three cases (Nos. 9,14 and 26). No other patient showed any sign of damage, clinical or radiological, to joints, although these were irradiated to the same dosage as the neighbouring bone. Movements in treated limb and spinal joints were in all cases full, free and painless. As yet, no case has been followed for more than twenty-two years and most have been observed over a much shorter period: it remains possible that these patients may tend to develop osteo-arthritis, especially where uneven irradiation has given rise to uneven bone growth and movement is taking place through an abnormally angled or uneven joint plane. This potential hazard will be discussed later.

Teeth.

The left side of the face of Case No.18. was irradiated when the child was two months old. When she was examined at the age of seven the teeth on that side, though well formed, were demonstrably smaller than normal, (Fig.7.) and her parent observed that they had erupted later than corresponding teeth on the unirradiated side. In other cases (Nos. 23 and 24)

Fig. 9.

Impaired muscular development following a course of radiotherapy. The patient was treated at the age of seven. There was remarkably little associated disability. (Case No. 3.)

Fig. 10.

aired development following radiotherapy to left axilla and lower neck. Note the lack of cutaneous tissue in the supra-clavicular hollow. The patient, who is an athlete, is left-handed. The nature of the infra-clavicular swelling is uncertain. (Case No. 7.)

treatment had been symmetrically applied to the face and, as there was no basis for comparison, it was not possible to assess the effect of irradiation. The permanent teeth in Case No.23, were small: Case No.24, was troubled by an unusual degree of dental caries which necessitated clearance of the mouth at an early age.

Muscle.

Impaired soft tissue development has frequently been reported in association with maldevelopment of bone (Gregl and Weiss,1961: Desjardins,1930: Vaeth and others,1962). The degree of impairment can be striking. Case No.3, was treated by radiotherapy to the leg at the age of seven. When she was thirteen the girth of the treated calf was eight centimetres less than normal and appearances suggested the gross atrophy that follows an attack of poliomyelitis (Fig.9.). There was, nevertheless, remarkably little interference with function: the power of the calf muscles appeared only slightly reduced and the child walked with little more than the trace of a limp. Almost all cases studied showed some lack of muscle development in the irradiated area and in each instance there was surprisingly little functional impairment. Case No. 7. (Fig.10.) was an excellent oarsman and swimmer despite considerable attenuation of the muscles of the left shoulder and Case No.9, was making an early name for himself as a runner, despite quite marked muscular asymmetry of buttock, lumbar region and abdominal wall. Patients were frequently oblivious of their deformity: Case No.6, was unaware of a six centimetre difference in the girth

of her thighs until she was twenty-five when her attention was drawn to the disparity by a dressmaker.

Although some degree of growth restraint was found in children irradiated at all ages, the effect was most marked in those under nine. It was not possible to distinguish from the available evidence whether changes were more marked for 230 KV or for megavoltage irradiation.

Irradiation of half the abdomen produced as characteristic changes in muscle as in bone: the rectus and paraspinal muscles were attenuated and the buttock was also less bulky than normal. Treatment of the neck also produced its own pattern: Fig. 8. shows the resulting thin neck with narrow sterno-mastoids and poorly developed trapezii, often associated with a pointed chin.

The effect of radiation on adult soft tissue has been described (Shields Warren (1942) surveyed the literature very comprehensively) and muscle is regarded as a very resistant tissue. No attention, however, has been paid to growing tissues and no histological descriptions exist. It is, therefore, impossible to do more than speculate regarding the nature of the developments following radiotherapy in children.

Impaired muscular development may be due to a damaged nerve supply, to disuse atrophy, to fibrosis, or to direct damage to the muscle cell. One could also suppose that the size of a muscle bears a direct relation to the related bone; it can be no wider than its attachments. There is no evidence to suggest radiation damage to the nerve cell or its end-plate, and mal-development of muscle following radiation is certainly not due

to disuse - Case No.7. showed definite changes in the left shoulder girdle although he was an active oarsman and swimmer, and left-handed. Change in muscle is not in all cases associated with under-development of bone - Case No.3. showed gross attenuation of the calf muscles although bones of leg and thigh were normal. In her instance there was probably some degree of muscle fibrosis, but fibrosis seems unlikely in Case No. 6, where the texture, contractility and function of the thigh muscles appeared entirely normal despite their considerably reduced bulk. It is tempting to postulate a direct action on the muscle fibre itself. Muscles increase in bulk with age or with strenuous exercise. The number of fibres present is probably constant from birth (Maximow and Bloom (1948)) and the thickness of the myofibrils themselves does not change: increase in width is due to accumulation of sarcoplasm, a heavily nucleated material which separates the myofibrils. Sarcoplasm is metabolically very active and its nuclei proliferate in response to muscle damage, being associated with digestion of dead tissue and repair. An active multinucleated tissue such as this often proves radiosensitive and it is reasonable to suppose that radiation may inhibit muscular growth by damaging the nuclei of the sarcoplasm. Dobrovolskaia-Zavadskaia (1924), quoted by Shields Warren (1942) stated that following "light irradiation" there was progressive diminution in the volume of the muscle fibre without much change otherwise. Her observation applied to adult tissue but it may possibly relate to a greater extent

Fig.11.

Impaired development of fat following radiotherapy. Chest and right side of abdomen were irradiated when the patient was six. At the age of eighteen there was so much asymmetrical fat on the left side of the abdomen that a mass was mistaken for a lipoma and excised. (Case No.14.)

Fig.12.

Relatively normal appearance of abdomen following irradiation to right side in adult life. Compare with Fig.11. which shows lack of fat development following irradiation to a similar dosage in childhood.

to growing muscle following radiation at therapeutic dose levels. The question might be solved by a muscle biopsy but we have not felt justified in obtaining this from any case in our series.

Fat.

Subcutaneous tissue also fails to develop fully following irradiation. This effect is seen in extreme degree in Case No. 14. (Fig.11.). This girl was treated when six years old by X-Ray therapy to half the abdomen for a nephroblastoma and the chest was subsequently irradiated for lung metastases. Subcutaneous fat developed to a moderate degree only in the irradiated areas of the trunk: in the sector of the abdomen that had not been treated, however, accumulation was so marked that a surgeon, unaware of the previous history, mistakenly diagnosed a lipoma and excised a mass of normal adipose tissue. The abdomen of another girl (Case No.10.) showed a similar appearance the effect was much less in boys, perhaps because they do not show the same tendency to develop fat on the trunk at puberty.

Adult fat is relatively resistant: Figure 12, showing the appearance of an abdomen half of which had been irradiated when the patient was twenty to a dosage of 3000r over four weeks, should be compared with Figure 11 which shows the picture following a similar dosage in childhood. Dosage of this order does not lead to clinically detectable fibrosis, and it seems likely that X-Ray therapy in children may damage the primitive mesenchymal cell or fibroblast that, according to Maximow and Bloom, may later take on a special function and become a fat cell.

Fig. 13.

Impaired development following radiotherapy to axillary glands when the patient was six. The edge of the field appears to have bisected the nipple. (Case No. 2.)

This effect of radiation suggests that more attention might with advantage be paid at the cellular level to the problem of obesity.

The Breast.

Breast development is readily inhibited by irradiation in infancy, a fact which has frequently been overlooked: severe hypoplasia, or apparently complete absence of breast tissue, has been reported on many occasions following radiotherapy to the chest wall (Gregl and Weiss, 1961; Ruhe, 1954). Moss stated that "during the pre-pubertal period, when the breast consists of a slowly expanding duct system, 1500r to 2000r (skin) through a single port over eight days will strikingly impair development, while 3000r to 4000r will produce severe fibrosis and shrinkage of the breast".

Case No. 2. was treated at the age of six by radiotherapy to the axilla: it seems likely that the edge of the field passed through the breast rudiment, the upper half of the breast receiving a dosage of 2600r in eight days (equivalent single fraction 1500r). The unirradiated half developed well while the irradiated portion showed little growth, the nipple being pushed upwards and outwards towards the axilla (Fig.13.). The patient has since borne five children and lactated, although breast feeding was not possible, owing apparently to flatness of both nipples.

Case No.28. showed imperfect development of the male nipple

following radiotherapy at the age of nine, (3500r in four weeks: equivalent single fraction 1300r).

Both breast rudiments of a six year old girl were involved when the whole chest of Case No.14. was irradiated, (3,500r in six weeks: equivalent single fraction 1150r). Some breast development was apparent when the patient was fifteen, but the breasts were still small when she was photographed at the age of eighteen. Some women who have never been irradiated do, of course, have small late-developing breasts, and this case merely serves to show that some development may take place after a dose of the order given.

Radiation Scoliosis.

The incidence of scoliosis following irradiation to the abdomen shows considerable variation between different series. A very high proportion of Rubin's cases (Rubin and others, 1962) showed some degree of deformity, while Neuhauser and others (1952) found scoliosis in only three of their patients, and I.G.Williams (1964) did not find the complication in any of a large series. Surprisingly, Rubin found that the degree of distortion was not related to the area treated - it was immaterial whether the whole abdomen or one side only was irradiated - and bore no relation to the severity of changes in the vertebrae. Scoliosis became apparent at an early date and, unlike idiopathic scoliosis, showed no deterioration after infancy. He was uncertain whether to attribute the condition

to changes in bone - vertebrae, ilium and ribs - or to impaired muscular development. All his cases were under eighteen months old at the time of treatment, an unusually young age distribution which may have accounted for the unduly high incidence of spinal curvature.

Experimentally, scoliosis can be produced by asymmetrical pressure on vertebral bodies or by damage to their epiphyses. Schwartzman and Miles (1945) and Bisgard (1935) produced a scoliosis by excising or denervating paraspinal muscles, and Wullstein (1902) brought about the same result by bandaging puppies in a position of curvature. Haas (1939) and Bisgard and Hunt (1936) caused spinal curvature by a one sided surgical attack on the epiphysis for the vertebral body, and Engel (1939) and Arkin and Simon (1939) produced scoliosis convex to the irradiated side by treating a lateral half of the growing spine with radium or X-Rays.

Experimental work then suggests two possible mechanisms of production of radiation scoliosis - by impairing muscular development or by causing asymmetry of bone. Only three of the Liverpool cases (Nos.8, 9 and 14) showed any degree of scoliosis, and in one of these (No.8.) the curve was in the thoracic region, which had not been irradiated, and convex to the treated side, whereas a radiation scoliosis is characteristically concave. All cases showed a good deal of impaired bone development. None was inconvenienced by or conscious of deformity. Although most irradiated cases showed some degree

of vertebral wedging, this was generally compensated by widening of the disc on the narrow side and did not result in curvature (Fig.5.).

Scoliosis appears to be an infrequent development and in our limited experience is not a troublesome disability.

THE CLINICAL SIGNIFICANCE OF IMPAIRED GROWTH RESULTING FROM
IRRADIATION: SUGGESTED MEASURES TO MINIMISE INCAPACITY.

Although many of the Liverpool cases showed an obvious degree of growth impairment, no patients - and few relatives - expressed any concern at cosmetic defects which were sometimes quite evident, and there was remarkably little associated morbidity. Symmetrical impairment was generally almost impossible to distinguish while an equal degree of deformity, if unilateral, was clinically obvious. Impaired development of neck and jaws following an even dosage to both sides by the 'bridge' technique was only apparent when several patients considered together were found to show the same growth pattern of pointed, tapering chin and thin neck: the defect following an equal dose to one side of the face or neck was obvious at a glance. Those patients in whom both sides of the abdomen were treated showed little apparent clinical or radiological change: when treatment was predominantly one-sided the resulting disturbance was generally obvious.

Observation periods have been relatively short, our subjects are still young, and it may be that secondary changes will develop in later years. The most serious late complication to be anticipated (apart from radiation induced malignancy, which is not relevant to this paper) is probably osteo-arthritis, which shows a particular liability to affect joints when normal mechanisms of movement are disturbed. While uniform irradiation

gives rise to an epiphysis which, though small, is normally shaped, uneven dosage results in uneven growth, with consequent disturbance of joint planes and axes: Bisgard and Hunt (1936) described an extreme varus deformity of the knee of a boy of fifteen resulting from treatment to the medial side of the joint ten years earlier. Reidy and his colleagues (1947) found damage to articular cartilage following irradiation: their observation has not been confirmed, but should it be true, any tendency to arthritis might be increased by direct radiation trauma to joint surfaces.

Osteo-arthritis has not been reported as a result of irradiation. It would, however, seem a reasonable precaution to ensure as far as possible that any necessary irradiation should be evenly applied throughout the extent of a growing epiphysis. In our series the effect of uneven irradiation is most apparent in those cases where half the abdomen was treated, resulting in wedging of vertebrae (Fig. 5.). One should aim, when prescribing for these patients, to treat the whole width of the spine: with modern megavoltage techniques this can be done more efficiently than in the past when the penumbra of an ortho-voltage beam gave rise to uncertainties in marginal dosage. If our suggestion (Page²³) that megavoltage radiation is less damaging to the epiphysis is correct, this would be another argument in favour of its employment.

Experimental work already quoted (Engel (1938), Reidy, Lingley, Gall and Barr (1947), Barnhard and Geyer (1962)), suggests that mechanical strain on the epiphysis leads to

tilting and uneven growth. In clinical practice, splinting and reduced weight-bearing activity in appropriate cases during and after courses of radiotherapy may be of value in reducing subsequent deformity.

It is obviously important when prescribing radiotherapy for children, to ensure that all radiosensitive structures are shielded as far as possible. There was probably no justification in our Case No.2. (Figs. 1 and 13) for irradiation of breast rudiment and head of humerus during the course of treatment to the axilla, and the gross shortening of the arm and maldevelopment of the breast are a monument to somebody's lack of foresight. This consideration applies, with special force, to the management of benign conditions which should be treated with the utmost discretion: keloids and haemangiomas should only be irradiated if they are particularly troublesome and there is no satisfactory therapeutic alternative. They should never be treated if they encroach on the nipple or overlies an epiphysis.

While every attempt should be made to avoid growth disturbance in children, radiation fields must always be adequate to cover the full extent of any tumour treated, whatever the risk to sensitive structures. It must never be forgotten that the aim of treatment is usually the cure of a fatal disease and that some degree of disability may well be the price of survival.

A P P E N D I X

CASE HISTORIES.

Cases 1 to 7	Irradiation involving limbs.
Cases 8 to 17	Irradiation of abdomen.
Cases 18 to 24	Irradiation of neck and jaws.
Cases 25 to 26	Irradiation of pelvis.
Cases 27 to 28	Irradiation of chest.
Cases 29 to 34	Irradiation of brain and spinal cord.

IRRADIATION INVOLVING LIMBS.

Case No.1. Female. Born 18.7.53.

Eosinophilic granuloma involving greater part of shaft of right femur. Biopsied.

16.2.59 to 9.3.59. X-Ray therapy to whole right femur.

Opposed 24 x 6 cm. fields. 4 MeV.

Skin dose 4000 rads. Midline dose 4000 rads.

19.1.66. Marked lack of development of muscles of right thigh and buttock. Mid-thigh girth 5 cm. less on right than on left.

Perceptible shortening of right thigh. Joint movements unimpaired. Slight limp. Unconscious of any disability.

X-Rays. R. femur. 6 cm. shortening. Osteoporosis of shaft.

Head and neck of femur smaller than on the left: premature fusion of irradiated epiphyses for head and trochanters.

Case No. 2. Female. Born 1937.

Lymphadenoma left axillary glands. Biopsied.

April 1943. X-Ray therapy to left axilla. Treated over 8 days.

Opposed 12 x 10 cm. fields. 230 KV.

Skin dose 2780 r. Midline dose 2,500 r.

1957. Pigmentation of skin, distribution suggesting that lower margin of field had passed through nipple. Nipple and areola small. Upper outer half of breast grossly under-developed. Left arm much shorter than normal. Marked lack of development

of muscle and sub-cutaneous tissue in irradiated area. Joint movements unimpaired. Not handicapped: good muscle power of shoulder.

X-Rays. Left shoulder girdle. Scapula and clavicle smaller than normal. Left humerus. 6 cm. shortening. Upper end small and osteoporotic.

1965. Patient had produced four children since 1957. Irradiated breast produced milk but breast feeding had been impossible owing apparently to defective nipples.

Case No. 3. Female. Born 19.7.51.

Ewings sarcoma, central shaft of left tibia. No biopsy.

7.7.59. to 8. 7.59. X-Ray therapy to shaft of left tibia, sparing epiphyses.

Opposed 20 x 7 cm. fields. 4 MeV.

Skin dose 1000 rads. Midline dose 1000 rads.

29. 7. 59. to 20. 8. 59. X-Ray therapy continued.

Skin dose 3500 rads. Midline dose 3500 rads.

Total dose 7.7.59 to 20. 8. 59.

Skin dose 4500 rads. Midline dose 4500 rads.

At the time of treatment the left tibia was two cms. longer than the right.

11. 1. 66. Marked lack of development of muscle in left leg.

Calf girth - left, 31 cm., right, 39 cm. No loss of muscle power. Slight limp.

X-Ray. Left tibia and fibula remain 2 cm. longer than right.

Otherwise no abnormality.

Case No. 4. Male. Born 4. 6. 50.

Cyst upper diaphysis of right humerus. Biopsied.

27.10.60. to 17.11.60. X-Ray therapy to upper half of right humerus.

Opposed 12 x 7 cm. fields. 4 MeV.

Skin dose 4500 rads. Midline dose 4250 rads.

At the time of treatment the right humerus was 7 cm. shorter than the left.

25.1.66. Negligible impairment of soft tissue development in irradiated area. No loss of power: joint movements normal.

X-Ray. Right humerus. 7 cm. shortening persists. Humeral head developing normally: epiphysis appears at same stage as that on opposite side.

Case No. 5. Male. Born 18.3.49.

Cyst midshaft left humerus. Biopsied.

30.11.61. to 30. 12.61. X-Ray therapy to midshaft of left humerus.

Opposed 14 x 10 cm. fields. 4 MeV.

Skin dose 4500 rads. Midline dose 4500 rads.

27.8.65. Muscles in irradiated area less well developed than normal. No loss of power: no disability.

X-Ray. Left humerus. No abnormality apart from disturbed trabeculation at original site of cyst.

Case No. 6. Female. Born 13.2.40.

Ewings sarcoma midshaft left femur. No biopsy.

21.8.53. to 27.8.53. X-Ray therapy to midshaft of left femur.

Opposed 20 x 10 cm. fields. 230 KV.

Skin dose 1050 r. Midline dose 1000r.

28.8.53. to 10.9.53. X-Ray therapy to whole left femur.

Opposed 35 x 10 cm. fields.

Skin dose 2200 r. Midline dose 2000 r.

30.10.65. Moderate growth impairment of soft tissues of left thigh: girth 6 cm. less than right. Subcutaneous fat attenuated as well as muscle. No loss of power. Patient unconscious of any disability.

X-Rays. 1.5 cm. shortening of left femur.

Case No. 7. Male. Born 8.5.46.

Lymphadenoma, glands left axilla. Biopsied.

10.2.61. to 3.3.61. X-Ray therapy to left axilla and supra-clavicular region.

Opposed 21 x 13 cm. fields. 4 MeV.

Skin dose 4500 rads. Midline dose 4370 rads.

12.8.65. Moderate developmental impairment of muscle and subcutaneous tissue of left shoulder girdle. Left arm shorter than right. No loss of muscle power: joint movements normal. An active, very athletic youth. Left-handed.

X-Rays. Left humerus - 2 cm. shortening. Epiphyses for upper end of both humeri symmetrically fused.

IRRADIATION OF ABDOMEN.

Case No. 8. Male. Born 3.6.52.

Nephroblastoma right kidney. Pre-operative irradiation.

12.12.52. to 26.1.53. X-Ray therapy to right side of abdomen.

Fields initially covered area from diaphragm to pubic symphysis and crossed midline: reduced in size later to cover diaphragm to iliac fossa and midline to flank.

12.12.52. to 5.1.53. Opposed 15 x 10 cm. fields. 230 KV.

Skin dose 1800r. Midline dose 1700r.

6.1.53. to 26.1.53. Opposed 10 x 8 cm. fields.

Skin dose 3200 r. Midline dose 2800 r.

27.3.53. Right nephrectomy.

January 1966. Markedly impaired development of abdominal and lumbar muscles in irradiated area: muscles of buttock affected to a lesser extent. Unconscious of any disability: spinal movements normal. Thoracic scoliosis concave to the right.

X-Rays. Pelvis. Markedly impaired development of right ilium. Epiphyses for irradiated femoral head and greater trochanter smaller than normal: epiphysis for lesser trochanter absent.

Lumbar spine. Wedging of vertebrae, narrowing to the right.

Right pedicles and transverse processes small. Short right 12th rib.

Case No. 9. Male. Born 12.12.58.

20.6.60. Right nephrectomy for nephroblastoma.

5.7.60. to 2.8.60. X-Ray therapy to right side of abdomen, fields extending from diaphragm to pubis and from flank across midline. Opposed 15 x 10 cm. fields. 230 KV.

Skin dose 3500r. Midline dose 3000r.

10.11.65. Soft tissue of right side of abdomen much less well developed than left. Rectus muscle and para-spinal mass about 1.5 cm. narrower on right than on left. "Wasp-waisting" on right side. An active athletic boy, a good runner, unconscious of any disability.

X-Rays. Pelvis. Right ilium much smaller than left, the distance between hip and sacro-iliac joints being shortened and the sacrum thereby tilted downwards to the right. Right sacro-iliac joint wider than normal: articular surfaces smaller than on the left.

Lumbar spine. Wedging of vertebral bodies narrowing to the right, with small pedicles and transverse processes. Mild scoliosis convex to left.

Case No. 10. Female. Born 2.11.45.

Pre-operative irradiation for nephroblastoma of right kidney.

2.5.47. to 12.6.47. X-Ray therapy to abdomen. Fields initially covered abdomen but were later reduced to irradiate right side, crossing midline.

2.5.47. to 18.5.47. Opposed 20 x 20 cm. fields.

Skin dose 1000r. Midline dose 900r.

19.5.47. to 12.6.47. Opposed 10 x 8 cm. fields.

Skin dose 1500r. Midline dose 1350r. 230 KV.

August 1947. Right nephrectomy.

28.10.65. Skin pigmentation of right side of abdomen with poorly defined margins. Markedly impaired development of muscles and sub-cutaneous tissue of right side of abdomen: right buttock slightly less well developed than left. Right iliac crest at a lower level than left. Spinal movements normal: no scoliosis.

A healthy young woman, conscious of no disability.

X-Rays. Pelvis. Moderate hypoplasia of right ilium. Both iliac crests show an epiphyseal scar, slightly more prominent on the left.

Lumbar spine. Wedging of vertebrae, narrow to the right. Small right lumbar transverse processes and pedicles. No scoliosis, the disc spaces being wider on the right and compensating for the deficiency of the vertebral bodies. Moderate hypoplasia of right lower ribs.

Case No. 11. Male. Born 15.4.57.

4.11.59. Resection of left half of a horse-shoe kidney for nephroblastoma.

24.11.59. to 28.12.59. X-Ray therapy to left side of abdomen.

Opposed 15 x 12 cm. fields. 230 KV.

Skin dose 3000r. Midline dose 2500r.

18.5.61. to 16.6.61. X-Ray therapy to whole chest for metastatic deposit at left hilum with pleural effusion.

Opposed 20 x 15 cm. fields. 230 KV.

Skin dose 2750r. Midline dose 2300r.

15.12.65. Impaired development of muscles of left abdominal wall and buttock: left abdomen about 1.5 cm. narrower than right. Poorly developed thoracic musculature: concave sternum. No complaints. Good general condition.

X-Rays. Pelvis. Slight growth impairment of left ilium.

Lumbar spine. Moderate degree of wedging of vertebrae. No scoliosis. Lower ribs symmetrically developed.

Case No. 12. Male. Born 1955.

19.1.59. Right hemi-colectomy for reticulum-cell sarcoma.

22.1.59. to 17.2.59. X-Ray therapy to right side of abdomen by opposed 15 x 10 cm. fields. 230 KV.

Skin dose 2800r. Midline dose 2600r.

12.1.66. Right abdominal musculature less well developed than left: slender right para-spinal mass. Right iliac crest lower than left. No scoliosis: spinal movements full and free. No complaints: a healthy boy, unconscious of any disability.

X-Rays. Pelvis. Poorly developed right ilium. As expected, no epiphysis as yet apparent for either iliac crest.

Lumbar spine. Slight wedging of vertebrae.

Case No. 13. Female. Born 23.11.48.

5.9.51. Right nephrectomy for nephroblastoma.

11.10.51. to 21.11.51. X-Ray therapy to right side of abdomen. Opposed 12 x 10 cm. fields. 230 KV.

Skin dose 3750r. Midline dose 3500r.

28.4.65. Reported well: not examined critically.

X-Rays. Pelvis. Moderate growth impairment of right ilium.

Lumbar spine. Slight wedging of vertebrae. No scoliosis.

Short right 12th rib.

Case No.14. Female. Born 18.3.48.

30.7.54. Right nephrectomy for nephroblastoma.

3.8.54. to 30.8.54. X-Ray therapy to right side of abdomen.

Opposed 15 x 12 cm. fields. 230 KV.

Skin dose 3500r. Midline dose 3450r.

16.11.54. to 16.12.54. X-Ray therapy to whole chest for metastatic deposits in right lung.

Opposed 20 x 20 cm. fields. 230 KV.

Skin dose 3000r. Midline dose 2900r.

16.11.54. to 16.12.54. X-Ray therapy to tumour mass in Pouch of Douglas. Opposed 8 x 8 cm. fields. 230 KV.

Skin dose 3500r. Midline dose 3000r.

In spite of the heavy dose to the pelvis the patient began to menstruate at the age of 14 although periods were still irregular when she was 17.

14.10.65. Gross asymmetry of abdomen owing to heavy accumulation of sub-cutaneous fat in the unirradiated area. A large mass of normal fat had been excised in mistake for a lipoma by a surgeon who was not in possession of all the facts. There was markedly reduced development of the muscles of the right side of the abdomen, the para-spinal mass and rectus

being particularly attenuated. Moderate lumbar scoliosis, convex to the left, correcting on flexion. Spinal movements perfect.

Healthy patient: no disability experienced.

X-Rays. Pelvis. Impaired development of right ilium.

Epiphysis for right iliac crest prematurely fused. Pubic symphysis widened, and articular surfaces out of alignment.

Sacral tilt downwards to the right.

Lumbar spine. Moderate degree of vertebral wedging.

Short right 12th rib.

Case No. 15. Male. Born 1945.

18.8.53. Left nephrectomy for nephroblastoma.

24.8.53. to 24.9.53. X-Ray therapy to whole abdomen.

Opposed 20 x 15 cm. fields. 230 KV.

Skin dose 3000r. Midline dose 3000r.

30.12.65. Abdomen possibly slightly narrower than normal.

Spinal movements normal. No complaints.

X-Ray. Pelvis. Iliac crests probably slightly shorter than normal. Lumbar spine normal.

Case No. 16. Female. Born 3.6.51.

1.10.62. Laparotomy and biopsy of fixed tumour mass in pelvis and lower abdomen - dysgerminoma of right ovary.

16.10.62. to 13.11.63. X-Ray therapy to pelvis and whole abdomen with left kidney shielded. Opposed 33 x 23 cm. fields.

4 MeV.

Skin dose 3000 rads. Midline dose 3000 rads.

16.2.65. No abnormality apparent on clinical examination.

Early breast development. Had not started to menstruate.

X-Ray. Pelvis normal. The epiphyses for the iliac crests have appeared symmetrically at their lateral ends.

Lumbar spine normal.

Case No.17. Female. Born 23.10.59.

22.4.52. Left nephrectomy for nephroblastoma.

19.6.52. to 16.7.52. X-Ray therapy to left side of abdomen.

Opposed 15 x 10 cm. fields. 230 KV.

Skin dose 4300r. Midline dose 4000r.

10.2.65. Slight pigmentation of skin in irradiated area.

"Wasp-waisting" on right side. Very slight reduction of bulk of left rectus and para-spinal muscles: very marked attenuation of fat in treated zone. Healthy: no disability.

X-Rays. Pelvis. Slight developmental impairment of ilium.

Lumbar spine. Slight wedging of vertebrae narrow to left side.

Lower ribs symmetrical.

IRRADIATION OF JAWS AND NECK

Case No.18. Female. Born 23.10.58.

Massive haemangioma of left side of face involving base of tongue. Thrombocytopenia: widespread purpuric haemorrhages. Tracheotomy.

6.1.59. X-Ray therapy to left face and upper neck.

Single 8 x 8 cm. field. 230 KV.

Skin dose 1000r. Dose at 5 cm. depth 580r.

14.1.59. X-Ray therapy to same field repeated.

Skin dose 500r. Dose at 5 cm. depth 290r.

12.1.60. Appearance normal.

25.11.65. Impaired development of left jaws and soft tissues of left side of face giving cheek a flatter contour. Left teeth smaller than right and later to erupt. Small left posterior cortical cataract.

X-Rays. Facial bones. Left side of mandible and maxilla smaller than right: teeth smaller on left side.

Case No.19. Male. Born 15.9.48.

Follicular lymphoblastoma glands of right neck. Biopsied.

17.2.58. to 15.3.58. X-Ray therapy to right side of neck.

Single 12 x 10 cm. field. 230 KV.

Skin dose 3750r. Dose at 5 cm. depth 2600r.

8.12.60. to 14.12.60. X-Ray therapy to left side of neck.

Single 12 x 10 cm. field. 230 KV.

Skin dose 2000r. Dose at 5 cm. depth 1400r.

12.1.66. Thin neck: attenuation of sub-cutaneous tissue in irradiated zones. Right sterno-mastoid slightly narrower than left, but power of muscles equal and normal: no torticollis.

Case No.20. Male. Born 1960.

Lymphadenomaglands both sides of neck. Biopsied.

9.4.64. to 29.4.64. X-Ray therapy to area extending from external auditory meatus to bifurcation of trachea by two opposed 15 x 12 cm. fields. 4 MeV.

Skin dose 3030 rads. Midline dose 2500 rads.

24.11.65. Clinically well. No bony or soft tissue change apparent.

Case No.21. Male. Born 15.5.47.

6.7.51. Mass excised from right side of neck.

Histological report: "Malignant Ganglio-neuroblastoma".

8.8.51. to 5.9.51. X-Ray therapy to neck and upper thorax.

Anterior 12 x 10 cm. fields with head turned to opposite side. 230 KV.

Skin dose 3500r. Dose at 5 cm. depth 2450r.

27.10.65. Pigmentation of irradiated skin. Narrow neck: ribbon-like sterno-mastoids. Manubrium sterni recessed, with suggestion of narrowing of thoracic inlet. No disability.

Case No.22. Female. Born 20.1.48.

Lymphadenoma glands right neck. Biopsied.

27.4.53. to 22.5.53. X-Ray therapy to right side of neck.

Single 10 x 8 cm. field. 230 KV.

Skin dose 4000r. Dose at 5 cm. depth 2700r.

30.12.65. Pigmentation of irradiated skin. Right sterno-mastoid ribbon-like. Sub-cutaneous tissue very thin in treated area. Right mastoid process smaller than left.

X-Ray. Cervical spine. Wedging of vertebrae, narrow on right side.

Case No. 23. Male. Born 1948.

Lymphadenoma glands left neck. Biopsied.

19.12.57. to 17. 1.58. X-Ray therapy by bridge technique.

20 x 10 cm. fields extending from zygoma to nipple. 230 KV.

Maximum dose 3250r. Minimum dose 2900r.

31.12.65. Face tapering from zygoma to a pointed chin. Jaws small, and teeth well formed but small. Thin neck. No disability.

Case No. 24. Male. Born 3.11.40.

Lympho-epithelioma involving nasal cavity and left antrum.

Biopsied.

14.12.49. to 11.1.50. X-Ray therapy by bridge technique.

20 x 10 cm. fields extending from zygoma to manubrio-sternal junction. 230 KV.

Maximum dose 3500r. Minimum dose 3440r.

Teeth all extracted for gross caries by 1960.

20.1.66. Small mandible and maxilla: face tapering from zygoma to a pointed chin. Thin neck with poorly developed musculature and sub-cutaneous tissue. Manubrium sterni recessed.

X-Rays. Skull. Mandible and maxilla hypoplastic. Retained immature lower third molars.

IRRADIATION OF PELVIS.

Case No. 25. Male. Born 1946.

Eosinophilic granuloma of right ilium. Biopsied.

18.11.48. to 8.12.48. X-Ray therapy to right ilium.

Opposed 9 x 9 cm. fields. 230 KV.

Skin dose 2550r. Midline dose 2500r.

19.1.60. Right buttock muscles less well developed than left. Right side of pelvis smaller than left. Right iliac crest and anterior superior spine lower than left.

X-Ray. Pelvis. Slight hypoplasia of right ilium. More marked growth impairment of upper end of femur, femoral head being small.

Soft tissue change altogether more conspicuous than bony abnormality.

Case No. 26. Female. Born 9.5.44.

15.12.59. Left salpingo-oophorectomy for adenocarcinoma of ovary.

9.1.59. to 2.2.59. X-Ray therapy to true pelvis.

Opposed 14 x 12 cm. anterior and posterior fields, opposed lateral 12 x 10 cm. fields. 4 MeV.

Maximum dose 4750 rads. Minimum dose 4600 rads.

20.1.66. No clinical abnormality on examination.

X-Ray. Pelvis. Pubic symphysis widened: articular margins of pubic bone rounded. Slight osteo-porosis of ilium, ischium and pubis in treated zone.

IRRADIATION OF CHEST.

Case No.27. Male. Born 1940.

13.2.53. Excision of neuroblastoma of right sympathetic chain in lower thoracic region.

18.3.53. to 17.4.53. X-Ray therapy to right lower thorax.

Opposed 15 x 10 cm. fields. 230 KV.

Maximum dose 4000r. Minimum dose 3150r.

7.2.66. Asymmetry of chest in treated area: right lower chest narrower than left. Pectorals and nipple normally developed.

X-Ray. Right lower ribs appear shorter than left.

Case No.28. Male. Born 24.4.42.

Large right paraspinal mass in lower right side of chest.

Needle biopsy - neuroblastoma.

26.3.51. to 20.4.51. X-Ray therapy to right lower chest by two opposed 15 x 10 cm. fields. 230 KV.

Skin dose 3400r. Midline dose 3000r.

24.6.63. Left thorax smaller than right. Marked lack of

muscle development in irradiated area. Irradiated nipple smaller than normal.

X-Ray. Chest. Poor film, badly centered. It does, however, suggest that right lower ribs are shorter and more oblique than left.

IRRADIATION OF BRAIN AND SPINAL CORD.

Case No. 29. Male. Born 1950.

Glioma region of third ventricle. No biopsy.

7.2.62. to 6.3.62. X-Ray therapy to brain. Whole calvarium treated by opposed 16 x 14 cm. fields. 4 MeV.

Skin dose 5000 rads. Midline dose 4700 rads.

12.12.65. No complaints. No abnormality apart from irregular growth of hair.

X-Ray. Skull. No bony abnormality attributable to irradiation.

Case No. 30. Male. Born 15.5.56.

Medulloblastoma posterior fossa. Explored and biopsied.

18.4.62. to 16.5.62. X-Ray therapy to brain. Whole calvarium treated by opposed 14 x 10 cm. fields. 4 MeV.

Skin dose 4500 rads. Midline dose 4200 rads.

14.7.65. X-Ray. Skull. Surgical defects. No abnormality attributable to irradiation.

Case No.31. Female. Born 19.2.45.

Medulloblastoma - clinical diagnosis. No biopsy.

5.10.56. to 15.11.56. X-Ray therapy to brain and spinal cord.
230 KV.

Skin dose 5100r.

Midline dose head and dose to vertebral bodies 3500r.

17.12.65. No abnormality apart from irregular growth of hair.
No spinal shortening demonstrated.

X-Ray. Skull. No abnormality.

Dorsal and lumbar spine. No abnormality.

Case No.32. Male. Born 5.12.57.

Ependymoma fourth ventricular region. Biopsied.

17.9.63. to 15.8.63. X-Ray therapy to brain and cervical
spine. Opposed 15 x 10 cm. fields. 4 MeV.

Skin dose 4000 rads. Midline dose 3950 rads.

15.12.65. X-Ray skull. Decompression and ventriculography
defects. Slight widening of lamdoidal suture.

Case No.33. Male. Born 27.4.48.

Cerebellar astrocytoma. Excised.

7.1.54. to 3.2.54. X-Ray therapy to posterior half of brain.
Opposed 12 x 10 cm. fields. 230 KV.

Skin dose 4375r. Midline dose 3570r.

17.11.65. No clinical abnormality apart from patchy growth
of hair.

X-Ray. Skull. Trephine openings. Otherwise normal.

Case No.34. Male. Born 31.12.58.

Medulloblastoma fourth ventricular region.

Clinical diagnosis. No biopsy.

24.10.62. to 9.11.62. X-Ray therapy to brain and spinal cord.

230 KV.

Skin dose 5100r. Midline dose skull and dose to vertebral
bodies 3500r.

22.12.65. No clinical abnormality apart from patchy growth
of hair. No demonstrable shortening of spine.

X-Ray. Skull, spinal column. No abnormality seen.

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