Clinical Radiobiology

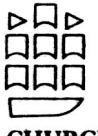
A. H. W. Nias

SECOND EDITION

Clinical Radiobiology

A. H. W. Nias MA, DM(Oxon), FRCR, MRCPath
Richard Dimbleby Professor of Cancer Research,
United Medical and Dental Schools,
St Thomas' Hospital,
London

SECOND EDITION



CHURCHILL LIVINGSTONE
EDINBURGH LONDON MELBOURNE AND NEW YORK 1988

CHURCHILL LIVINGSTONE
Medical Division of Longman Group UK Limited

Distributed in the United States of America by
Churchill Livingstone Inc., 1560 Broadway, New York,
N.Y. 10036, and by associated companies, branches
and representatives throughout the world.

First published 1977
Second edition 1988

ISBN 0-443-03340-4

British Library Cataloguing in Publication Data
Nias, A. H. W.
Clinical radiobiology. — 2nd ed.
1. Man. Cancer. Radiobiology
I. Title II. Duncan, William, *1930–*
616.99'40642

Library of Congress Cataloging in Publication Data
Nias, A. H. W.
Clinical radiobiology/A. H. W. Nias. — 2nd ed.
Rev. ed. of: Clinical radiobiology/W. Duncan, A. H. W. Nias. 1977.
Includes bibliographies and index.
1. Radiobiology. 2. Radiotherapy. I. Duncan, William, 1930–
Clinical radiobiology. II. Title.
[DNLM: 1. Radiobiology. WN 610 N577c]
RM849.N53 1988
616.07'57 — dc19

Produce by Longman Singapore Publishers (Pte) Ltd.
Printed in Singapore

Dedication

To Bibi, who has been so patient.

Preface

The need for this book was expressed in the preface to the first edition, which was jointly written with Professor William Duncan in 1977. At that time we noted that, 'It is now essential for radiotherapists to have a sound basic knowledge of radiobiology'. 'The Royal College of Radiologists, London, requires that radiotherapists in training have formal instruction in radiobiology'. 'The material in this book is designed to cover the syllabus recommended by the College and has been written with a deliberately clinical bias. As a result, many of the more fundamental principles of radiobiology have received comparatively little attention in this book, while many aspects of applied radiobiology have been emphasized because they have direct relevance to clinical practice'.

Although the book is written primarily for the clinician who wishes to have some understanding of the basic biological principles of radiotherapy, it is hoped that it will prove of value and interest to others involved in the treatment of cancer. Nowadays, this includes the use of cytotoxic drugs and I have added material to this edition to illustrate some of the similarities between chemobiology and radiobiology.

Our policy in 1977 was to concentrate on those principles of the subject which are well established and so I have not found it necessary to make radical changes. Nevertheless, the science of radiobiology has advanced and so I have made a thorough revision to bring the book up to date, particularly in those aspects of clinical importance. The clinical chapters had originally been written by Professor Duncan and he made many helpful suggestions for this edition but I take responsibility for the whole text. My colleagues Drs Thelma Bates and Oliver Scott have read the new clinical and radiobiological sections, and I am grateful for their constructive suggestions.

The final typing of the manuscript was undertaken with great speed and accuracy by Debbie Katz. Her cheerful attitude to my many additions and alterations transformed a daunting task into an enjoyable experience and I am most grateful to her. I also thank the staff of Churchill Livingstone for all their help in producing this book.

London, 1988 A.H.W.N.

Acknowledgement

I would like to thank the many colleagues who generously and willingly gave permission for diagrams and illustrations from their published work to be reproduced in this book.

Contents

Preface	vii
1. Introduction	1
2. Biophysical events	7
3. The biological target	22
4. Biochemical damage	42
5. Cell survival curves	56
6. Modification of cell survival	76
7. Recovery from cytotoxic damage	96
8. Early response of normal tissues	113
9. Total body syndromes	129
10. Response of tumours	145
11. Late effects on normal tissues	161
12. Fractionation	180
13. Clinical applications	201
14. Experimental therapy	226
15. Risks and safety	253
Index	276

1

Introduction

The practice of radiotherapy is founded almost entirely on the experience and carefully documented clinical observations of skilled and studious radiologists over the last 70 years. Only recently has its basic science, radiobiology, begun to influence the understanding and development of the clinical applications of radiations used in cancer therapy and the subject is now a compulsory part of the training of radiation oncologists. The reasons for this apparently late influence are of interest and are best explained by a short account of the history of radiobiology.

The origin of the subject was the discovery of X-rays by Professor Wilhelm Conrad Röntgen in the University of Würzburg. The announcement on 28 December 1895 of this new type of radiation attracted immediate interest throughout the world. In the next year Henri Becquerel, a French physicist, reported to the Academy of Sciences in Paris on the 'emanation' from uranium, and soon afterwards Marie and Pierre Curie were able to isolate radium and introduced the concept of 'radioactivity' to the world of science.

In 1934 the first artificial radioactivity was produced by Frederic Joliot and his wife Irene, daughter of Marie Curie. The 'atomic age' was born with the demonstration of nuclear fission by Hahn and Strassman in Germany.

The early years of the development of radiotherapy were dominated by the improvements made in radiation physics, engineering and technology. It was obviously essential to have safe and reliable X-ray machines with energies capable of sufficient penetration in tissues to treat deep-seated tumours. Methods of accurate radiation dose measurement had to be evolved to ensure the consistent exposure of the area to be treated.

A major advance was achieved with the manufacture of the Coolidge hot filament tube in America in 1913. This generator was able to provide for the first time a controlled and reliable output of X-radiation and was to be the model for future orthovoltage X-ray generators which became available in the early 1920s. There followed in 1932 the production of the first cyclotron, the Van de Graaf high-voltage generator and in 1940 the devel-

opment of the linear accelerator for the production of megavoltage X-radiation and electron beams.

For many years the measurement of dose depended on chemical dosimetry, estimated by a change of colour as in the *Sabouraud et Noire* pastille unit. The system was difficult to standardize and many biological methods were used to supplement the chemical estimation of radiation exposure. A common practice was to determine the 'skin erythema dose' which produced a reddening of the skin in 1 or 2 weeks after irradiation. This too was wholly unsatisfactory, but it was not until 1928 that the röntgen (R) unit was accepted internationally as the measure of ionization in air. Further improvement in clinical dosimetry was later realized with the introduction in 1954 of the rad, the unit of 'radiation absorbed dose', and the SI unit, the gray was introduced in 1978.

In spite of the technical difficulties and limitations of the primitive X-ray generators, many forms of experimental treatment were tried at the earliest opportunity. Within 4 months of Röntgen's discovery Dr Daniels in the United States reported in April 1896 the loss of hair in one of his colleagues following irradiation. It is usually claimed that as a result of this report the first rational application of X-ray therapy was given by Dr Leopold Freund of Vienna, who successfully treated a benign hairy naevus in 1897. It may be that the first use of radiation in cancer therapy took place earlier in January 1896 when E. H. Grubbe, a physicist at the Hahneman Medical College in Chicago, claimed to have treated a patient with breast cancer referred to him by Dr Ludram (Hodges 1964). Reports of other miscellaneous applications were soon published, but it was not until 1922 that radiotherapy could be recognized as a defined clinical discipline with a significant contribution to make in cancer control. It was in this year that Regaud and colleagues reported the results of a series of patients with cancers of the larynx before the International Congress of Otology in Paris.

During the early days of experimental research and clinical practice employing X-rays, some unfortunate results of over exposure were observed, especially on the skin of radiologists and X-ray workers. These, and other pathological changes that had been reported, encouraged extensive research on the pathology of radiation injury in all the organs and tissues. The work was essentially descriptive and qualitative and several important original reports and comprehensive monographs on radiation pathology were produced at this time (Warren 1928, Desjardins 1931).

Soon after reliable X-ray equipment became available in the 1920s radiation research workers began to examine the nature of the biophysical events produced in tissues by X-rays. Initially the main interest lay in the effects of direct ionization in the track of the radiation. It soon became clear that ionization produced indirectly by the radiation as a result of free-radical formation, principally by the radiolysis of water, was also of great importance. In this period many important basic studies were conducted by Lea in England and Zimmer in Germany. Their research culminated in the

development of the 'target theory' of radiation action which was to lead to the quantitative evaluation of radiation effects on cells and important advances in radiobiological research.

The dramatic breakthroughs in radiobiology which have encouraged a most productive era of research came in the 1950s when in-vitro cell culture techniques were perfected and the era of quantitative cellular radiobiology was entered. At the same time increased concern and interest in the hazards of atomic radiation gave further impetus to the expansion of radiobiological research. There were now available reliable radiation sources, consistent dosimetry and a whole new range of quantitative techniques in cell biology. In 1953 Howard & Pelc identified the DNA synthetic phase in the cell cycle. This laid the foundation for studies of cell population kinetics.

Another phenomenon which is of major importance in radiobiology is the 'oxygen effect', first described in detail by L. H. Gray and his colleagues also in 1953. Oxygen is the most powerful radiation sensitizer that has so far been described. The demonstration that many tumours contain a proportion of anoxic cells has led to the conclusion that these cells are relatively radioresistant by virtue of their anoxicity and may be the cause of failure in cancer control by radiotherapy. It is known that many types of cancer that originally have anoxic foci, improve their oxygenation during, and as a result of, fractionated radiotherapy. Many experimental clinical approaches have been advocated to reduce the radioresistance of anoxic cells in tumours. In 1955 Churchill-Davidson and colleagues first introduced the use of hyperbaric oxygen inhalation to improve tumour oxygenation before irradiation with X-rays and this method continues to be evaluated.

Then in 1956 Puck & Marcus used their new culture technique for single mammalian cells to demonstrate the exponential relationship of radiation dose to decreasing cell survival. These experiments were followed by a series of important discoveries which introduced radiobiologists and their clinical colleagues to a new language to describe the response of cells and tissues to radiation and to new concepts about the biological basis of radiotherapy. In this period it should be recognized that the contribution of radiobiology to clinical radiotherapy was mainly conceptual and few practical applications based on laboratory findings were considered suitable for evaluation in clinical trials. Indeed, the contribution of radiobiology to radiotherapy has often been to elicit a mechanism to explain an empirical clinical observation.

The serious effects of cancer are caused mainly by the progressive accumulation of the abnormal cells in the patient. The object of radiotherapy is to sterilize the tumour or to cause *loss of reproductive integrity* of the cancer cells. This term implies that the cell has lost its capacity for unlimited proliferation although the injured cell may retain the ability to go through several cell divisions before finally dying. During this time the cell will apparently be morphologically intact and differentiated cells may function. For example, a thyroid cell may continue to produce its complex

hormone, just as it did before it was lethally irradiated. The mammalian cell will normally die in mitosis after a lethal dose of radiation. For this reason rapidly dividing cells will show evidence of radiation damage more quickly than cells with long cell cycle times. This was observed as long ago as 1906 by Bergonie & Tribondeau (probably the first radiobiological observation in history). So, the rate of response of cells to radiation injury is related to the rate of turnover, and it is not the cells themselves, but the processes of cell division that are sensitive to the effects of radiation.

In 1959, Elkind & Sutton had elegantly demonstrated that mammalian cells possess the ability of *recovery from sublethal radiation damage* and that when recovery is complete the cells respond to subsequent doses of radiation as if they had never been irradiated. This is undoubtedly one of the most important fundamental processes in the response of cells to radiation and was of immediate relevance to radiotherapy. The 'wasted' radiation used in producing repairable damage explains in the main the need to increase the dose of radiation when many dose fractions are given. Also differences in degree of 'recovery' between some tumour cells and some normal-tissue cells may be the single most important factor in explaining the selective eradication of the cancer cell population compared to normal tissues in successful radiotherapy.

The use of high linear energy transfer (LET) radiation, such as fast neutrons, had been proposed by L. H. Gray and colleagues in 1940. Clinical trials with fast-neutron beams have been completed in a few centres and other accelerated nuclear particles such as negative pi mesons and light atomic nuclei are also available for clinical application. The fact that cells are less able to recover from high-LET radiation damage was then shown by cellular radiobiologists and this explained the overdosage problems that had beset the early neutron therapists in the 1940s.

The main benefit of neutron therapy was presumed to follow the other radiobiological consequence of high-LET radiation: the reduction in the oxygen effect, so that hypoxic tumour cells are relatively less radioresistant. An analogous mechanism was then suggested by Adams & Dewey (1963) who showed that electron-affinic drugs can mimic the effect of oxygen and make hypoxic cells more radiosensitive. None of these radiobiological strategies have shown a consistent radiotherapeutic benefit so far and the simplest solution may still prove to lie in a regime of fractionation which takes most advantage of re-oxygenation between treatments.

The scheme of fractionation is often individual to different schools of radiotherapy and there are no generally agreed optimum regimes for different types of cancers. However, the pattern followed today is that established by Coutard in 1934 when he developed a 'protracted fractional' method and there has been little evidence produced since then to suggest that daily fractionation may be disadvantageous. The contribution of radiobiologists to this subject began with Strandqvist (1944) who related total

dose to number of fractions. Then Ellis (1965) separated overall time from number of fractions. More recently the different time-dose relationships of early- and late-reacting tissues have been demonstrated. There is still much need for further detailed study of fractionation schemes in clinical use, but the economic consequences of unnecessarily prolonged fractionation are obvious.

Clinical radiotherapy has been practised as a defined medical specialty since the mid-1920s, when the first deep X-ray therapy machines became available. Radiobiology has been recognized as a distinct scientific discipline for a much shorter time. Since 1940 impressive technological advances in the related fields of physics, chemistry and biology have provided the means for radiobiological investigations on a scale and in detail unattainable before. In this period remarkable progress has been made in our understanding of the action of radiation on cells and tissues (Lea 1955, Zimmer 1961, Elkind & Whitmore 1967, Alper 1979). This book attempts to describe these discoveries and to relate their implications for clinical radiotherapy.

REFERENCES

Adams G E, Dewey D L 1963 Hydrated electrons and radiobiological sensitisation. Biochemical and Biophysical Research Communications 12: 473–477

Alper T 1979 Cellular radiobiology. Cambridge University Press, Cambridge

Becquerel H 1896 On various properties of the uranium rays. Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences 123: 855–861

Bergonie J, Tribondeau L 1906 Action des rayons X sur le testicle. Archives d'Electricite Medicale 14: 779–791, 911–927

Churchill-Davidson I, Sanger C, Thomlinson R H 1955 High pressure oxygen and radiotherapy. Lancet 1: 1091–1095

Coutard H 1934 Principles of X-ray therapy of malignant disease. Lancet ii: 1–8

Desjardins A U 1931 Action of roentgen rays and radium on normal tissues. American Journal of Roentgenology 26: 1–90

Elkind M M, Sutton H 1959 Radiation response of mammalian cells grown in culture I. Repair of X-ray damage in surviving Chinese hamster cells. Radiation Research 13: 556–593

Elkind M M, Whitmore G F 1967 The radiobiology of cultured mammalian cells. Gordon & Breach, New York

Ellis F 1965 The relationship of biological effect to dose-time fractionation factors in radiotherapy. Current Topics in Radiation Research 4: 357–397

Gray L H, Morgan J D, Read J, Spear F G 1940 Some experiments upon biological effects of fast neutrons. British Journal of Radiology 13: 371–375

Gray L H, Conger A D, Ebert M, Hornsey S, Scott O C A 1953 The concentrations of oxygen in dissolved tissues at the time of irradiation as a factor in radiotherapy. British Journal of Radiology 26: 638–648

Hodges P C 1964 The life and times of Ernie Brubbe. University of Chicago Press, Chicago

Howard A, Pelc S R 1953 Synthesis of deoxyribonucleic acid in normal irradiated cells and its relationship to chromosome breakage. Heredity (suppl 6): 261–273

Lea D E 1955 Actions of radiations on living cells, 2nd edn. Cambridge University Press, Cambridge

Puck T T, Marcus P I 1965 Action of X rays on mammalian cells. Journal of Experimental Medicine 103: 653–666

Regaud C, Coutard H, Hautant A 1922 Contribution en traitement des cancers endo larynges par les rayons. Xth International Congress d'Otology: 19–22

Röntgen W C 1895 Über eine neue Art von Strahlen. Erste Mitteilung. Sitzungsberichte der Physikalische Medizinischen Gesellschaft in Würzurg: 132–141

Strandqvist M 1944 Studien uber die kumulative Wirkung der Röntgenstrallen bei Fraktionierung. Acta Radiologica 55 (suppl): 1–293

Warren W S 1928 The physiological effects of radiation upon normal body tissue. Physiological Review 8: 92–129

Zimmer K G 1961 Studies in quantitative radiation biology. (Transl H. D. Griffith) Oliver & Boyd, Edinburgh

2

Biophysical events

In this book we assume a knowledge of basic radiation physics and that the reader has made a study of the principles involved in the generation of ionizing radiations (e.g. in a textbook like *Fundamental Physics of Radiology* by Meredith & Massey, 1978). Radiation energy may be dissipated in the process called *excitation* in which an electron is raised to a higher energy level. This is all that happens with the longer wavelength radiation in the ultraviolet range (Fig. 2.1). When the radiation has an even shorter wavelength, its energy is transferred by both excitation and *ionization*, ionization being the removal of an electron from its atom or molecule. This chapter will be primarily concerned with those biophysical events which are the consequences of the interaction of ionizing radiations and matter.

THE RADIATIONS AND THEIR INTERACTIONS WITH MATTER

X- and gamma-rays

Still the most commonly used in clinical radiotherapy, these are electromagnetic radiations consisting of streams of energetic photons (or packets of energy) which can cause ionization. X-rays are produced when a stream of fast electrons is stopped in a block of metal, usually tungsten. The energy of the resultant electromagnetic radiation depends upon the energy of the electrons, as well as the atomic number of the metal. Following interaction of these two factors, photons with a range of energies are produced. The resultant beam of X-rays will therefore have a range of wavelengths but each interaction results in radiation with a 'characteristic wavelength'.

Figure 2.1 shows a comparison of the wavelengths of various sources of radiation on the left, with the diameters of various biological objects on the right. X- and gamma-rays fall at the lower end of this diagram, having very short wavelengths. The 'characteristic wavelength' determines the peak energy of the radiation beam generated by a particular X-ray tube and this energy is described in the units of peak kilovoltage, kVp. Because gamma-rays result from discrete nuclear disintegrations they have a single energy. In all other respects, X- and gamma-rays have similar properties when they

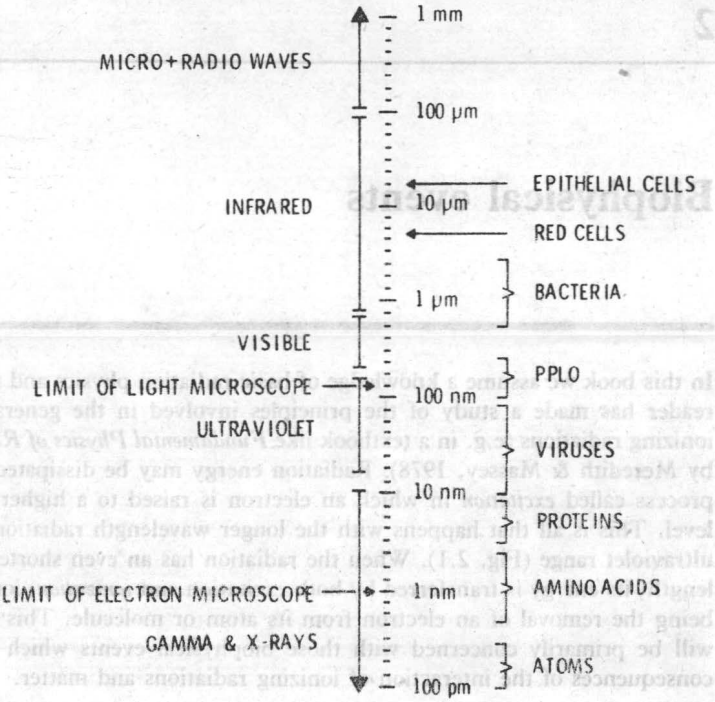


Fig. 2.1 Scale of radiation wavelengths and target sizes (PPLO = pleuropneumonia-like organisms)

interact with atomic matter. From a biological viewpoint the tissues of the body include 'targets' of varying atomic number. Furthermore the mechanisms of interaction between radiation and these 'targets' will apply to ionizing radiations of all types, including neutrons and accelerated charged particles, which deposit their energy by a nuclear interaction which also depends upon the structure of the target atoms.

The transfer of energy from electromagnetic radiation to matter is effected by one or more of three processes of attenuation which depend upon the energy spectrum of the radiation. At energies less than 0.5 MeV the predominant method of interaction is by the *photoelectric effect* in which the photon is completely absorbed by the target atom; an electron is emitted and 'characteristic' radiation is produced. This process is of less interest and importance to radiotherapists now that megavoltage X-ray generators and gamma-ray sources (with a peak energy greater than 1 MV) have largely replaced orthovoltage equipment in clinical practice. Compton scattering and pair production are then the main types of interaction.

Compton scattering is predominant over the energy range 0.5 MeV to 5 MeV and is illustrated in Figure 2.2 which shows the neutrons and

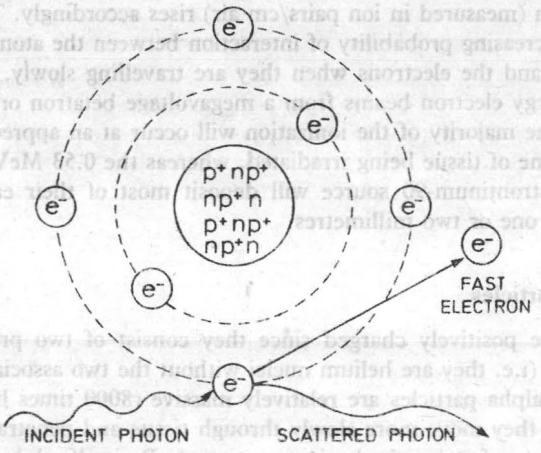


Fig. 2.2 Compton scattering (from Hall 1988)

protons which form the nucleus of an atom together with the planetary electrons. In the Compton process the incident photon collides with a planetary electron, a recoil electron is produced and the 'scattered' photon leaves with diminished energy. Depending upon its energy this photon may then interact with additional target atoms by further Compton scattering or by the photoelectric effect.

Pair production occurs at photon energies in excess of 1.02 MeV but it only begins to be of biophysical importance with X- and gamma-irradiations above 20 MeV peak energy. The incident megavoltage photon is converted into an electron and a positron. The latter is a positively charged electron which is eventually annihilated by collision with an ordinary negative electron to produce two photons of energy 0.51 MeV, which are called annihilation radiation.

Electrons

External electron sources are also used in clinical radiotherapy, and the attenuation of electrons is clearly an important process because the three methods of absorption of photons just described all involve the production of electrons. These particles (called beta particles in the context of radioactive disintegrations) are negatively charged and have very small mass. Because of this, electrons will be easily deflected from their track by other electrons. A tortuous track will result so that the *range* of an electron (or the depth to which it penetrates) will be much less than its true track length. What is important to note, however, is that the greatest density of ionization occurs at the end of this track. The velocity of the electron falls as its energy is degraded to a few tens of electron volts and then the specific

ionization (measured in ion pairs/cm air) rises accordingly. This is because of the increasing probability of interaction between the atoms of the target material and the electrons when they are travelling slowly. In the case of high-energy electron beams from a megavoltage betatron or a linear accelerator, the majority of the ionization will occur at an appreciable depth in the volume of tissue being irradiated, whereas the 0.53 MeV beta particles from a strontinum-90 source will deposit most of their energy within a depth of one or two millimetres.

Alpha particles

These are positively charged since they consist of two protons and two neutrons (i.e. they are helium nuclei without the two associated electrons). Because alpha particles are relatively massive (8000 times heavier than an electron) they move more slowly through tissue and penetrate only a short distance — a few hundred microns at most. By itself, alpha radiation is of little importance in radiotherapy but since the mixed emission from many radionuclides includes alpha particles their mode of action merits description. Furthermore, they are produced by fast neutrons and negative pi mesons in tissue. As with electrons, the greatest density of ionization occurs at the end of the alpha-ray track but this will be short and straight (in contrast to an electron track). This is because the low velocity and the double charge permits more ionization to occur. Thus an alpha particle is very densely ionizing. In terms of *linear energy transfer* (LET) units of keV per μm length of track, the average value along the track would be about

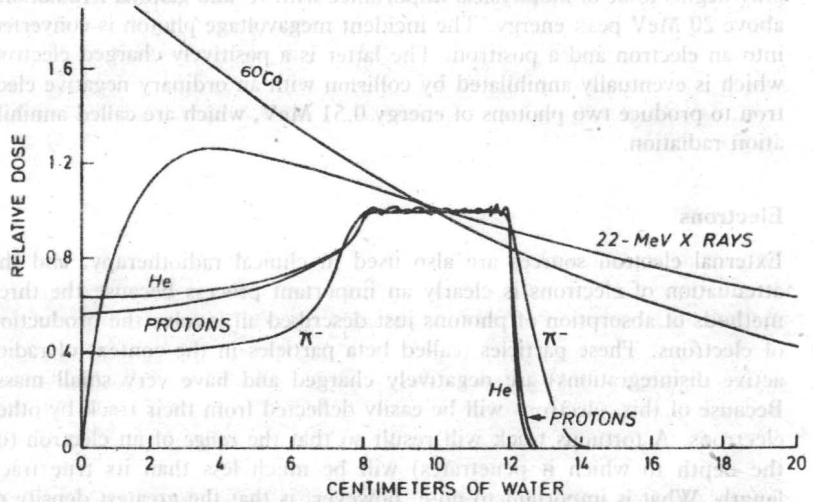


Fig. 2.3 Central-axis depth-dose distributions of cobalt-60 gamma-rays, 22 MeV X-rays, protons, helium ions and negative pi mesons normalized to 50% dose at 10 cm (from Raju & Richman 1972)