PROGRESS IN NUCLEAR ENERGY

SERIES VII

MEDICAL SCIENCES

VOLUME 1

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SERIES VII

MEDICAL SCIENCES

Titles of the eight series

Series I	PHYSICS AND MATHEMATICS
Series II	REACTORS
Series III	PROCESS CHEMISTRY
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Series V	METALLURGY AND FUELS
Series VI	BIOLOGICAL SCIENCES
Series VII	MEDICAL SCIENCES
Series VIII	ECONOMICS AND ADMINISTRATION

NOTE

In reference lists and elsewhere "Geneva Conference Paper" refers to papers presented at the International Conference for the Peaceful Uses of Atomic Energy, held at Geneva, in August, 1955.

FOREWORD

By Robert S. Stone

While a faint dawn of insight into the use of nuclear energy in medicine appeared at the turn of the century when some applications of the natural radioisotopes to medical problems were developing, the real sunrise started in the nineteen thirties when artificial radioisotopes were produced in limited quantities by cyclotrons. The full light of day came when nuclear reactors made available large quantities of radioisotopes of many elements. In the early forties the fact that so many isotopes of so many elements were available in large quantities was necessarily a military secret. Hence "security measures" shrouded even medical uses in a haze until the Geneva Conference on Peaceful Uses of Atomic Energy cleared the atmosphere and provided once again for the free flow of information between the scientists of all nations.

The desire to help the sick of whatever nation has always been so great that the interchange of medical knowledge has continued when that of other sciences has stopped. It was no surprise, therefore, to find that no startlingly new medical discoveries had been concealed until the Geneva Conference. There was, however, a flood of information that had been acquired in various countries by the new tools and new techniques. Volume 7 of this series on the Progress of Nuclear Energy gives an insight into this new knowledge.

The ionizing radiations from radium and X-ray tubes have been used as therapeutic tools for over half a century. It was natural therefore to find that much attention had been focused on how the newly available radioactive materials could be used as therapeutic tools. With the single exception of the method of using radioiodine, no radical departures from previous techniques have been put forth. The hope of finding a method of selectively localizing a radioisotope in cancer cells wherever they might be in the human body has not yet been realized. While the new methods made possible by the new materials have beyond doubt given comfort to many patients, no great advance toward the cure of cancer has been made as yet.

A note of warning should be sounded at this stage of development. The availability of radioisotopes for therapeutic purposes has increased at a much greater rate than the availability of physicians with adequate training in their use. It is possible that more harm than good may result before sufficient numbers of trained personnel are available.

The field of greatest usefulness to medicine of radioisotopes is that of applying tracer techniques to obtain more insight into the workings of the body in both health and disease. The new isotopes have made possible great advances in this sphere. Most of the research of this type is reported in the volume dealing with the Biological Sciences—but it is impossible to draw a line between these two disciplines. The research techniques developed in the laboratory become diagnostic when taken to wards and clinics. Several diagnostic procedures using radioisotopes have become standard in medical practice and were reported from many countries. The up-to-date endocrinologist cannot practise intelligently without the information he receives from tests using radioiodine. Many haematologists like to know about the iron metabolism as determined by radioiron. Internists study blood volume, circulation time, electrolyte balance and other functions by the use of radiochromium, radiosodium, radiopotassium and others. In the field of cancer control the chances are great that humanity will profit much more from the knowledge gained about the growth of cancer by the use of radioactive materials as tracers than it will from their use as therapeutic agents.

One of the great advantages of investigations using radioisotopes is that such small quantities are needed that there is little or no interference with the processes being studied. To measure smaller and smaller quantities of ionizing radiations has been the aim of those interested in instrumentation. In this field a lot of ideas were exchanged at Geneva.

It is necessary to have universally understood units of measurement if all parts of the world are to be able to compare results. The problems of dosimetry were dealt with at length and are reviewed in this volume.

The author of this foreword considers that its object should be to stimulate the reader's interest in a thorough study of this volume by giving some idea of the stimulus that started it on its way, of the purpose it is intended to serve and of the subject matter that it contains. The stimulus was the obvious need for a critical summary of the great amount of scientific material that was presented at the Geneva Conference. The purpose is to make the essential facts readily available to you who want them. A glimpse of the subject matter has been given here and in the foreword by Sir Ernest Rock Carling. The cold details are given in the table of contents and in all the pages of this volume—to which you, the reader, can now proceed.

FOREWORD

By Sir ERNEST ROCK CARLING

PROGRESS in the search for knowledge has never gone hand in hand with immunity from hazards. Constraint of ionizing radiation to human purpose has had its martyrs, but if the seeds of progress, for their maturation, demanded the blood of pioneers, a stage has been reached when continuing advance should entail no further sacrifices. There must be reasonable freedom from danger for those who devote their lives to work in the nuclear energy field. Protection, in that field, calls for much fundamental information as yet available only in part.

The occasion from which this series of books has sprung was one for restatement of what has already been won, and for comparison of the winnings of one nation with those of another. This was truer perhaps of the biological and medical sciences than of applied physics and engineering. Publication of radiotherapy methods had been unrestricted.

Be that as it may, there was a common atmosphere of pressing on towards badly needed further experimental research. It was not so much pride of achievement that resounded, but a call to more strenuous collaborative effort. That set the note of the discussions at Geneva. There was the sense of a harvest of gain for the human race waiting to be gathered.

Almost half a century before atomic bombs burst on the world, the hazards to man innate in radioactive sources were recognized. At that time the quantum of natural radioactive material in earth, air and sea was hardly so much as guessed at. Even today it is not generally appreciated how colossal are the amounts of radioactive potassium and carbon in man's environment that hitherto have gone undetected. When it is realized, and then related to the mediums of distribution, some idea of the scale of dilution to which quantities dispersed by detonations must be subject can be gained, and a proper judgment made of the minuteness of the resultant levels of world-wide danger.

Reassuring as the facts prove to be, it is clear nevertheless that with reactors set up in every quarter of the globe—as they may be—there will be quantities of effluents and waste products to be dealt with that are not beneath comparison with those threatened by major accidents or hostile action. There will in fact be a public health problem of world-embracing magnitude. For its understanding all available information, such as this series of books seeks to present in its latest accumulation, must be taken under consideration.

It is by no means a simple matter to formulate an account of the phenomena. Given an understanding of the physical basis of irradiation, it is still a problem how best to measure, and to record the form and quantum of energy under discussion. Dosimetry, which here is dealt with by FAILLA, is of primary importance. It must be admitted that there is as yet incomplete agreement among experts as to the proper units to employ for particular purposes; and in regard to an irradiated individual how to sum for biological effects doses which are measured in different units. It is one of the objects of such Conferences as that at Geneva to reach at least approximate agreement on the best method permitted by current knowledge.

Where effects may be separated from presumed causes by thirty or more years it is idle to attempt finality of description today. Though we are now aware of some of the delayed results of bygone treatments we cannot rely upon the contemporary records for dose measurements, which at that date were certainly imperfect and may often have been grossly erroneous. However, there have been international contacts enough, even though they have not been world-wide, to give assurance that what is said in these papers is acceptable in the main to all experts. A very considerable literature on the mechanisms of radiation injury to organic tissues, and of the modes of injury to human beings, has accrued from animal research as well as from clinical experience.

As in so many fields, observation of the results of pathological processes preceded appreciation of physiological error or deficiency; in no other field has physiology depended to the same degree on chemistry and physics, which in turn have been illuminated by the isotope tool, as will be fully realized from the contributions of MAYNEORD and BELCHER, and ROSS. Indeed there is scarcely an article which is not dependent for its argument upon data so derived. The field of genetics has been largely illuminated by those studying radioactive phenomena, which have been experimentally employed for elucidation of chromosome breaks and gene mutations. Research on ionization as a factor in the complicated molecular chemistry of cytoplasm and nucleus in active metabolism has proved rewarding.

When we turn to more general applications of radioactivity for the benefit of mankind the possibilities in the agricultural field assume great importance. Food production must be increased to keep pace with population increases. Although as a general proposition it must be admitted that gene mutations are predominantly harmful, yet it is possible for the agronomist to breed and select plants adopted to soils and climates otherwise infertile for food production and thus to increase an area under cultivation.

Quite apart however from genetic possibilities of that kind, the isotopic tool offers great opportunities. It can trace the soil elements actually absorbed, their route and utilization, and determine the fertilizing additions necessary to increase crop yield. Isotopic tracing of the habits and methods of spread of pests of all kinds is now feasible and will permit effective control, so that losses whilst growth continues and also when the storage stage is reached can both be minimized. There is promise of increased crop yield and of diminished wastage.

This volume also deals with protection against radiation hazards, in both its aspects, avoidance of exposure when necessarily stationed where danger lies, and with possible modification of the biological effects induced by ionizing radiation reaching the tissues. The principle of avoidance is simple—intervention of a dense medium. The application is of extreme complexity, demanding the greatest ingenuity to reconcile extremely precise and often delicate manipulations with the necessity for distance and a massive volume intervening. Nor is that all. No mechanical perfection suffices to ensure safety. Conduct must conform impeccably to imperative rules, and that is attained only with an education competent to lend habitual activities the certainty of a reflex.

The late Dr. CIPRIANI was thoroughly conversant with the day-to-day oversight maintained by Health and Physics and Medical Departments of establishments dealing with all the stages of radioactive substances production, with all ranges of hazard, and with the problems of disposal of solid liquid and gaseous waste products. That the atomic energy establishments have functioned with extremely few accidents, and with an average level of exposure of all those employed well below that currently accepted as permissible, is eloquent witness to the understanding by all those engaged, whether in design, engineering, construction, or utilization of massive and delicate apparatus, of the high potency of radioactive substances for lethal action.

The article on the principles and standards of radiation safety is from the pen of BINKS (than whom probably no one is better informed). He is the Secretary of the International Commission on Radiological Protection. The Report issued by that body is the combined effort of experts of many countries. The fundamental data, so far as they are known to date, there find publication. No one is more accurately aware of the deficiency in our knowledge than those who have drawn up the tables.

A great effort is being put into developing methods of measuring body-burden of extraneous active substances. The background radiation due to cosmic and terrestrial sources is enhanced by that due to the potassium of the body itself and sets a task of great difficulty.

Even when the total body-burden is measured it is still important to know in which organ of the body a substance lodges by preference, and that may vary according to the method of entry. It is essential to know not only the physical but also the biological half-life of all isotopes. It is necessary to know, for each isotope, what is the critical organ which unfortunately is not necessarily the organ in which the greatest concentration occurs. Naturally most study has been devoted to the most important (which means the most dangerous or the most frequently used) isotopes, but some 150 have been scheduled under various pertinent aspects.

BINKS is also concerned with the essentially practical day-to-day criteria of safety in radiological departments and laboratories. Hitherto legislative sanctions, save as a part of regulations for factories employing or producing toxic substances generally, have been imposed only in one or two countries.

In a field expanding with great rapidity, and one in which knowledge and experience are accumulating with use, it is difficult to frame regulations that have the force of law without imposing restraints that would sterilize initiative. There is the alternative of the issue of Codes of Conduct, adapted to the circumstances of various institutions, hospitals, laboratories, factories. Observance of them is not obligatory, but neglect of their recommendations would undermine a defence against claims for damage by employees or others.

Hitherto the proportion of the population occupationally exposed has been small, but circumstances are changing and dangers are becoming more dispersed.

Industry is rapidly adapting radioactivity to its purposes; quantities for transport by land, sea and air are increasing; apparatus of enormously increased potentialities is being built; quantities of waste for disposal will eventually assume very serious proportions. In face of such developments it behoves all concerned with the prevention of harm to the race to familiarize themselves with the dangers and the means of forestalling them.

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1

RADIOACTIVE ISOTOPES IN MEDICAL DIAGNOSIS

By E. H. BELCHER and W. V. MAYNEORD

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INTRODUCTION

Abstract—The applications of radioactive isotopes in medical diagnostic and tracer investigations have increased notably in the past five years. In this review the status of radioactive isotope techniques in diagnostic practice is examined with particular reference to the papers on this subject presented before the Geneva Conference on Peaceful Uses of Atomic Energy, 1955. The physical basis of radioactive tracer techniques is first discussed, and methods used for the radioactive assay of biological samples and measurement of uptake of radioactive materials *in vivo* are described. Specific applications of these techniques in diagnosis are then reviewed in detail. These include the use of radioactive isotopes in dilution techniques to measure the volume of the blood and other compartments of the body, in the study of red cell life span and blood circulation problems, in the detection and localization of tumours, as radiographic sources, and in the assessment of functional state of many organs and tissues of the body.

THE STATUS of radioactive isotope techniques in diagnostic practice finds expression in the papers on this subject presented before the International Conference on the Peaceful Uses of Atomic Energy at Geneva, August 1955. The purpose of this review is to survey the present situation with particular reference to the papers read at this conference. In so wide a subject the reviewer must exercise a rigid selection, and in view of the wealth of published material that has appeared in the past five years he cannot make any attempt at an exhaustive bibliography. Nevertheless, in order to cover the field as widely as possible, reference will not be limited to the papers read at the Geneva Conference, but rather will these be used as a framework on which to display the more established diagnostic procedures and to indicate those developments which are most likely to prove of value in the foreseeable future. References in the text to papers read at Geneva will be denoted by an asterisk after the date.

The potentialities of artificially radioactive isotopes in radiation therapy were early recognised and exploited. Their application to medical diagnostic and tracer investigations was not realised so rapidly, except in a few isolated techniques such as the use of radioactive iodine in the study of thyroid function. The past five years, however, have seen increasing interest in the diagnostic uses of radioactive materials, notably in physiological and biophysical studies. The reasons for this belated but increasing awareness of the value of isotopic techniques in diagnosis must be sought in a number of causes. Most diagnostic techniques with isotopes are essentially tracer studies, wherein the radioactive atoms follow the same metabolic pathways as do their normal inactive counterparts in the body. They must therefore be introduced into the living organism at a specific activity low enough not to influence the processes whose course one desires to study. Because of the low neutron fluxes in early reactors, specific activities available were often low, and moreover the measuring techniques then used were frequently insensitive. Uncertainty about radiation hazards and lack of information about localization of different elements in the body tissues led to unnecessarily large safety factors in the maximum permissible doses of different isotopes. As a result, many investigations were precluded that are now possible. Nowadays, because of higher neutron fluxes and the use of enriched materials, isotopes can be produced at specific activities much higher than hitherto, and still greater improvements can be predicted. Improved assay methods and in particular the development of the γ-scintillation counter have reduced the radioactive dose necessary for effective sample assay. More detailed metabolic knowledge has also increased the maximum permissible dose of many isotopes used. The present situation is well summarised in the reviews by HASTINGS (1955),* FATEYEVA (1955),* MAYNEORD (1955)* and WARREN (1955).*

In order to be of value in diagnostic applications, a radioactive isotope should have a physical half life long compared with the duration of the investigation in which it is to be used, but a biological half life sufficiently short for it not to constitute a radiation hazard to the recipient. It should also satisfy the criteria of availability at high specific activity and at a high degree of radiochemical purity, and the radiations which it emits should be readily detectable using simple equipment. In Table 1 are given details of the isotopes most commonly used in diagnostic and tracer studies and which satisfy these requirements to a greater or lesser extent.

Table 1—Radioactive Isotopes of Value in Diagnostic and Tracer Studies

Isotope	Type of radiation	Half-life	Energy of radiation (MeV)	
			β-particles†	γ-rays
H^3	β^-	12·5 y	0·018	
C^{14}	β^-	5600 y	0·155	
F^{18}	β^+	112 m	0·65	
Na^{22}	β^+, γ	2·6 y	0·54	1·28
Na^{24}	β^-, γ	15·1 h	1·39	1·37, 2·75
P^{32}	β^-	14·3 d	1·70	
S^{35}	β^-	87·1 d	0·17	
Cl^{36}	β^-	$4{\cdot}4 \times 10^5$ y	0·71	
Cl^{38}	β^-, γ	37·3 m	4·81, 2·77, 1·11	1·60, 2·15
K^{40}	β^-, γ	$1{\cdot}3 \times 10^9$ y	1·33	1·46
K^{42}	β^-, γ	12·4 h	3·58, 2·04	1·51
Ca^{45}	β^-	152 d	0·25	

† Maximum energy.

Table 1—Radioactive Isotopes of Value in Diagnostic and Tracer Studies (cont.)

Isotope	Type of radiation	Half-life	Energy of radiation (MeV)	
			β-particles†	γ-rays
Cr^{51}	K, γ	27·8 d		0·33
Mn^{52}	K, β⁺, γ	6·0 d	0·58	0·73, 0·94, 1·46
Mn^{56}	β⁻, γ	2·58 h	2·81, 1·04, 0·65	0·82, 1·77, 2·06
Fe^{55}	K	2·94 y		
Fe^{59}	β⁻, γ	45·1 d	0·46, 0·26	1·10, 1·30
Co^{56}	K, β⁺, γ	72 d	1·50	0·84, 1·26, 1·74, 2·01, 2·55, 3·25
Co^{57}	β⁺, γ	270 d		0·12, 0·13
Co^{58}	K, β⁺, γ	72 d	0·47	0·81
Co^{60}	β⁻, γ	5·27 y	0·31	1·17, 1·33
Cu^{64}	K, β⁻, β⁺, (γ)	12·8 h	0·57 (β⁻) 0·66 (β⁺)	(1·35)
Zn^{65}	K, (β⁺), γ	250 d	(0·32)	1·12
As^{74}	β⁻, β⁺, γ	17·5 d	1·36, 0·69 (β⁻) 1·53, 0·92 (β⁺)	0·60, 0·63
Br^{82}	β⁻, γ	35·9 h	0·46	0·54, 0·61, 0·69, 0·77, 0·82, 1·03, 1·31
Kr^{85}	β⁻, (γ)	9·4 y	0·69, (0·15)	(0·54)
Rb^{86}	β⁻, γ	19·5 d	1·82, 0·72	1·08
Sr^{85}	K, γ	65 d		0·51
I^{131}	β⁻, γ	8·1 d	(0·81), 0·61, 0·33, 0·25	0·08, (0·16), 0·28, 0·36, 0·64, 0·72
I^{132}	β⁻, γ	2·3 h	2·2, 0·9	0·69, 1·41, 2·0
Xe^{133}	β⁻, γ	5·3 d	0·34	0·081
Cs^{134}	β⁻, γ	2·3 y	0·65, 0·09	0·56, 0·60, 0·79, 1·04, 1·16, 1·36
Tm^{170}	β⁻, γ	127 d	0·97, 0·88	0·085
Au^{198}	β⁻, γ	2·69 d	0·96	0·41

† Maximum energy

METHODS OF PHYSICAL MEASUREMENT

Sample Assay Methods

The use of radioactive isotopes in diagnostic techniques involves the radioactive assay of samples of blood, excreta and tissue specimens, and also in many cases the measurement *in vivo* of uptake of the isotope by organs of the body. In any diagnostic procedure the radiation dose to the patient must always be kept as low as possible, and restrictions to the permissible dose of the isotope often stringently limit the usefulness of possible techniques. It is important, therefore, that the detection and assay methods should be as sensitive as possible. The methods of sample assay used in diagnostic work do not differ essentially from those used for other types of radioactivity measurement, and for a description of these techniques the reader is referred to standard textbooks (LOW-BEER, 1950; SACKS, 1953; COMAR, 1955). Glass and metal-walled G-M counters, ionisation chambers and scintillation counters of varying design are all used routinely, though no single advance in the past decade has had more far-reaching consequences in the diagnostic field than the development of the scintillation counter for γ-measurement. The calibration and maintenance of such sub-standard apparatus has been described by SINCLAIR, TROTT & BELCHER (1954). Especial mention may be made of the well-type scintillation counter incorporating a thallium-activated sodium iodide crystal (ANGER, 1951), which by virtue of its high detection efficiency together with the fact that it can be used with equal ease to assay solid or liquid samples has found particular favour in diagnostic procedures.

Autoradiographic techniques for the localization of radioactive materials at the cellular level in tissue specimens (BOYD, 1955; FITZGERALD *et al.*, 1953) have also been found useful in certain types of investigation, but are limited in diagnosis by the high dose needed to produce a good autoradiograph.

The Measurement of Radioactive Uptake in vivo

Uptake *in vivo* of radioactive isotopes may be measured by collimated G-M or scintillation counters placed on the surface of the body. Because of the short range of β-particles in body tissues such techniques are usually restricted to γ-emitting isotopes. In certain instances small probing counters may be introduced into body cavities.

In many diagnostic procedures it is useful to know not only the total amount of radioactivity in an organ of the body but also the spatial distribution of that activity. This may be found by moving a counter manually over the region of interest and plotting the results in the form of a diagram in which "equinumeral" lines join points having the same counting rate, but such techniques are time-consuming and tiring to both subject and operator, and often inaccurate. Considerable effort has therefore been spent on the design of scanning systems which perform the same task automatically; the possibilities and limitations of such systems are reviewed by CASSEN & BAUER (1955)* and MAYNEORD (1955)*.

The optimum design of a scanning system necessitates a compromise between the requirements of spatial resolution, contrast, dose level, time required to scan a given area, and scaling factor (the number of counts producing one pulse in the recording system). Spatial resolution depends on the nature and