Progress in
ATOMIC MEDICINE

VOLUME 1

Edited by

JOHN H. LAWRENCE, M.D., D.Sc., F.A.C.P.,

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GRUNE & STRATTON

New York London

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GRUNE & STRATTON

New York London

Library of Congress Catalog Card No. 65-12654

GRUNE & STRATTON, INC.
381 Park Avenue South
New York, New York

Printed in U.S.A. (K-A)

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Preface

IT IS now over 30 years since the disco ery of artificial radioactivity and the development of the cyclotron which made available for the first time medically useful quantities of radioactive elements and new sources and types of radiation. Their value in medical research and diagnosis was quickly realized, and in 1937, when radioactive phosphorus was first used to treat a patient, the era of Atomic Medicine was born. The development of the atomic reactor during World War II thereafter made many artificial radioactive elements easily and widely available. From the beginning, Atomic Medicine has been a rapidly growing field, this being largely due to the valuable radioactive tracer technique which revolutionized research methods, leading to the better understanding of many basic biological processes. Radioisotopes have made possible many new diagnostic methods; furthermore, teletherapy with x rays and gamma rays has been aided by the new tele-therapeutic sources of gamma rays such as cobalt 60, and heavy-particle beams produced by cyclotrons have been successfully used in the treatment of metabolic, neurologic, and neoplastic diseases.

In this first edition of PROGRESS IN ATOMIC MEDICINE we have tried to select topics to illustrate the value of the products of atomic energy in several different areas of medical research, diagnosis, and therapy, and have included examples of research and diagnostic studies using the isotope tracer technique, isotope scanners and cameras, whole-body counters, shortlived isotopes and positron emitters, and activation analysis, as well as examples of the therapeutic uses of isotopes, cobalt-60 gamma rays, and heavy particle beams.

The Editor is grateful to the contributors for their willingness to undertake the task of writing the chapters in this first volume, to the publishers for their patience and helpfulness, and especially to Miss Janice DeMoor for her able and patient editorial assistance.

JOHN H. LAWRENCE, M.D.

Contents

CHAPTER 1

The Whole-Body Counter in Medical Research and Diagnosis

By STANTON H. COHN, PH.D.

THE EXTRAORDINARY GROWTH of the number of whole-body counters throughout the world since 1949 reflects a response to the need for a sensitive system for in vivo determination of low levels of radionuclides. A graph of data from a recent survey[1] of the numbers of presently functioning whole-body counters for the period 1949 to 1961 shows the growth of the number of counters as an exponential function with a doubling time of approximately 2 years. There are at present over 100 counters in use or under construction around the world.[2] The remarkable development of whole-body counting systems and the concomitant multiplication of its applications clearly indicate its usefulness as a scientific tool. One of its most important applications is, of course, in medical research.

If the present growth rate is maintained, 10,000 whole-body counters will have been constructed by the year 1977. Practically, however, the growth is limited by the number of centers interested in medical research and health physics, by the high cost of the instrument ($50,000–100,000), and by the skilled man power required for its operation. On the other hand, when radioactive materials come into more general use as power sources, large numbers of whole-body counters will be required to monitor specific populations and to stand ready for assays of accidental contamination, in what will conceivably be a more radioactive environment. Other factors which will tend to increase the number of counters are decreasing cost as a result of increasing production, and greater ease in maintenance, particularly as transistorized equipment and standardized units are employed.

Widespread interest in the use of whole-body counters is also indicated by the fact that within the last few years three major symposia

Research supported by the U.S. Atomic Energy Commission.

have been held on this topic. Two symposia entitled "Radioactivity in Man" were held in the United States in 1960[3] and 1962,[4] and in addition an international symposium sponsored by the I.A.E.A. was held in Vienna in 1961.[5] A recent I.A.E.A. symposium which discussed whole-body counting techniques was held in Heidelberg in 1964.[5A]

Historically, whole-body counters have gained in accuracy, precision and sensitivity since the first ionization chamber measurements of radium by Schlundt,[6] as pointed out in a review by Spiers.[7] Particularly significant contributions to the development of present systems were made by Evans[8] and Sievert.[9,10] The former developed many of the present measurement techniques, while the latter constructed the first very sensitive large 4π high pressure ionization type counter.

As it became possible to make reproducible determinations of very low levels of radiation, and thus to follow the retention of tracer doses of isotopes, the whole-body counter evolved as a practical tool for medical research. An excellent bibliography of some 300 references on all phases of the development of whole-body counters and the growth of their applications in the past 30 years has been compiled by the I.A.E.A.[11]

This review will consider whole-body counting systems designed for medical research and their applications. A number of studies employing these systems have been carried out to date, and a survey of these studies yields considerable information regarding the unique opportunities for research afforded by whole-body counting. It is also possible to delineate the limitations of present systems and to outline as yet unexplored areas for research. Illustrations of these points will be made with details from various research projects. The author has drawn heavily from work carried out at the Brookhaven National Laboratory, since requisite details were most readily available; however, similar studies have been carried out at a number of centers, and reference is made to these throughout the report.

The popularity of whole-body counters as a tool in clinical research stems largely from the relative ease of measurement, the speed of determination and the accuracy in the results. These attributes have contributed to the greatly increased quantity of studies which formerly required tedious and difficult measurements of blood and excreta, and to a simultaneously improved quality of the studies. As the human gamma spectrometer has been developed, there has been a parallel development in the use of automatic systems for recording and analyzing the greatly increased outflow of data. The most current and sophisticated equipment available for recording data as well as high-speed digital computers are now employed in conjunction with whole-body counting systems. The combination of reliable whole-body counters with computing equipment for analysis has greatly enhanced the speed and reliability with which in vivo studies of tracers can be carried out.

Instrumentation and Shielding Requirements for Whole-Body Counters for Medical Research

There are several basic designs for whole-body counters with a number of minor variations. However, there is no general agreement at this time as to the type of counter best suited for a particular application.

Counters may be classified according to three basic types, based on differing detectors and differing counting geometries. These are as follows:

The sodium iodide crystal detector used with the "standard chair" geometry which was developed to its present state largely by Marinelli and Miller[12-14] at Argonne National Laboratory.

The liquid scintillant detector (in which the detector is a liquid scintillant in a double-walled, hollow cylindrical tank) with the subject placed in a supine position in a 4π geometry was developed largely by Anderson[15-18] at Los Alamos National Laboratory.

The plastic scintillation detector with the subject generally placed in a supine position was developed largely by Burch[19,20] at Leeds.

Only the sodium iodide crystal detector type of counter (Fig. 1) will be considered in this review. It is the most versatile system for medical research, and for this reason, in addition to its superior spectrometric properties and ease of operation, it is at present the most widely used system.

In a comprehensive survey made by the I.A.E.A. in May 1962 of 69 whole-body counters located at various places in the world, using sodium iodide crystal detectors,[1,2] 55 percent employed a fixed single NaI (Tl) detector with standard-chair geometry similar to that devised by the Argonne group. The second most popular system is that with fixed multi-crystal detectors and bed-type geometry (21 per cent). The remaining 24 percent used scanning systems of detection, either employing single or multi-crystal detectors.

Types of Crystal Detector Systems: For clinical research studies, the choice presently appears to lie between single-fixed position detectors and movable multi-detector systems. Each system has advantages and disadvantages, and these are a function of the particular application.[21] The single, large 8″ x 4″ crystal is less expensive, requires simpler associated electronic data pick-up and recording systems and is easier to operate, particularly in long-term studies in which the original counting geometry must be reproduced a number of times. It is, however, particularly difficult to calibrate for studies in which isotopes concentrate in specific organs.

The multi-detector system offers the advantages of greater sensitivity and of being less subject to geometry-efficiency calibration problems, as will be discussed in some detail. The multi-detector system with smaller crystals has the further advantages of being able to localize the distribution of radionuclides. The disadvantages reside in calibration uncertainties and in more complex (and therefore more expensive) and more difficult to maintain electronic circuitry. Further, it is difficult and time-consuming to determine the optimum placement for the crystals for new studies. Recently a computer program was devised to make this placement determination in a manner so as to yield a fairly linear detection response.[22] This approach promises to make movable multi-detector systems more feasible for general use.

Components of Whole-Body Counters

The primary advantage of whole-body counting over radiochemical determination of body burdens of isotopes lies in the ability of the former system to detect very low levels of tracers, and thus to permit the use of very low doses of isotopes in patients. It is, therefore, of the utmost importance to maintain the highest possible over-all signal-to-noise ratio in the system. This ratio is determined by the operating performance of each of the components of the system: the detector, the shielding, the associated electronics, and the arrangement of subject and detector (the counting geometry). These will be considered separately.

Detectors: Monte Carlo calculations on the efficiencies and the photofractions for gamma rays in various sizes of sodium iodide crystals indicate that the highest efficiency is obtained with the larger sized crystals.[14,23] In the gamma-ray energy range of 0.5 to 2.5 MeV, the single crystal of large diameter, 8″ to 9″, and 4″ thickness provides the detector of choice. With these large crystals, the use of multiple small phototubes

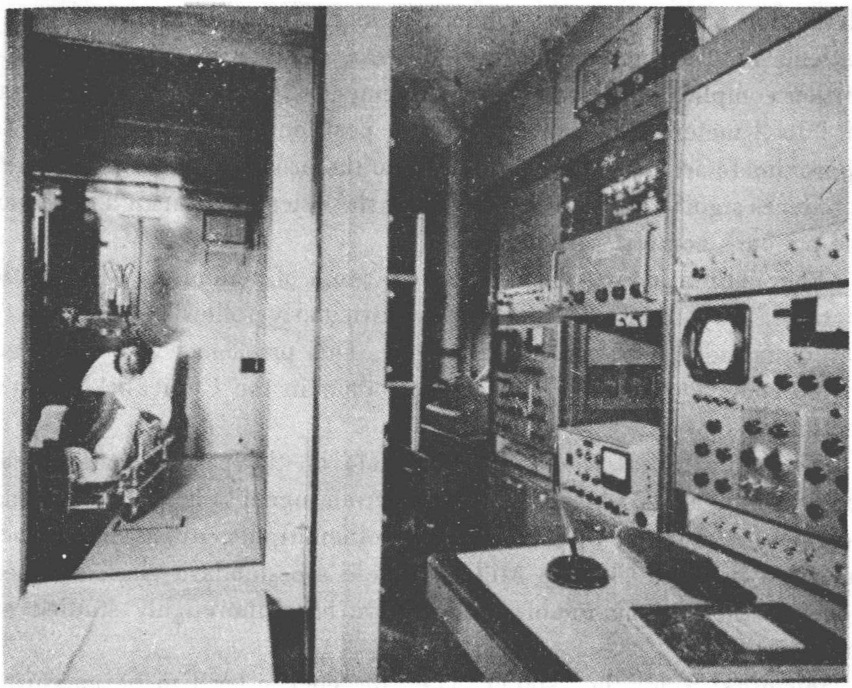

Fig. 1. Brookhaven whole-body counter with subject positioned under NaI (T1) crystal detector. Pulse-height analyzers and associated electronics seen at right.

gives the best resolution for the system.[14] In multi-detector systems, 5″ x 4″ crystals appear to satisfy best the requirements for high efficiency simultaneously with practical considerations of size (and related cost).

Counting Geometry: An optimum position of detector with respect to the patient is 22 to 25 inches over the apex of the tilting chair. A geometry used at BNL for medical applications which is similar to that devised at Argonne employs an ambulance cot which can be adjusted into a "standard chair" geometry (Fig. 1). The cot has wheels and a urethane foam mattress. The cot may easily be rolled out of the counter and returned quickly and simply to a fixed position, in which it is then locked. Thus it has facilitated the counting of nonambulatory patients. The position of the chair, however, results in difficult calibration problems which have not as yet been completely resolved.[14,24] The calibration difficulties arise from the complex geometry required for efficient counting of the human body. The differences in scatter and selfabsorption of the primary gamma ray in its interaction with tissues of patients of different heights, weights and habitus are problems which further complicate calibration.[24,25] Placement of the detector at a distance of 1 to 2 meters from the patient and positioning of the patient in an approximate arc provides one solution to the problem, but, unfortunately, it reduces significantly the sensitivity of the detection system and reduces the patient's comfort as well.

Other calibration problems occur as a result of nonuniform distribution of tracers, a situation which occurs particularly following oral or even parenteral administration of an isotope. This problem will be discussed in the context of specific experimental data in the Clinical Application section.

Electronic Circuitry: Considerable data on the performance of electronic components which affect the over-all signal-to-noise ratio (pulse-height analyzers, amplifiers and photomultiplier tubes have been reviewed by Marinelli and Miller.[14] These are standard electronic components whose signal-to-noise ratios have been thoroughly studied and minimized.

Shielding: Since the "signal" (i.e., the energy level to be measured) is low, the background noise must be reduced to a minimum value, as determined by the practical considerations of cost and convenience. Thus, all counters are operated in a shielded environment. Steel is the most commonly used shielding material; it appears to be the most constant and versatile. Lead, water, concrete, chalk and Dunnite have also been used for shielding, but are generally less desirable than steel for a number of reasons. The background in a steel room with walls of optimal thickness (6 to 8 inches of steel) with single 8″ x 4″ NaI crystal averages 1500 counts/minute. The size of the room affects the background level because of the scatter of radiation from the walls into the detector, so that a large room is desirable. A large room is also desirable from the point of view that it permits greater flexibility in experimental set-ups. A thin lead lining is generally used in conjunction with the steel walls to reduce the low energy components (below 0.5 MeV) of the background. Cadmium and copper linings have also been used in addition to lead to further reduce this low energy component.

Limits of Detection

The over-all signal-to-noise ratio determines the limits of detection of a particular system. The minimum detectable in vivo activity for a 20-minute count in an average man (containing 140 g of potassium and 10 mμc of cesium-137), using a single 8″ x 4″ crystal in the standard type of steel and lead shielding and a standard tilting-chair geometry is approximately 1 mμc.[1] This is for gamma rays of energy 0.3 to 1.5 MeV which is the energy range of the common tracers used in medical research. (The detection limit is here defined as three times the statistical standard error of the net counting rate in the photopeak region.) The detection limits range from 10^{0} to 10^{-5} of the maximum permissible body burdens (mpbb) of various radionuclides, and 10^{-3} to 10^{-5} of the mpbb for most clinically important radioisotopes.[1] Although the present limits of detection can probably be lowered by further developments of the components: photomultipliers, pulse-height analyzers, detectors, shielding, etc., the present development of the whole-body counter is far superior to other contemporary techniques for measurement in metabolic studies.

Automatic Data-Handling and Computer Analysis of Whole-Body Counter Data

The nature and volume of the output data of whole-body counting systems virtually require the use of automatic data-handling techniques and computer analysis of complex gamma spectral data. A number of computer methods have been reported for analyzing these data.[26,28] In general, these programs reduce the data to a form suitable for computer analysis, using paper punched tapes and cards, or magnetic tapes.

A technique called "gamma stripping" is employed to separate the complex gamma spectra into the specific components of various energies. In general, this is done by removing, one at a time, the components associated with each energy peak by comparison with previously-determined calibrated spectral data. In each successive step, one component is removed and the resulting curve calculated until by this "stripping" process the entire curve is analyzed. The process is complicated by the fact that there is a certain scattering—Compton distribution of low energy components—associated with the photopeaks, which must be taken into account.

In some programs, calibration factors are introduced to take into account stature and habitus and counting geometry of the subject.[27] In one study, for example, the gamma-ray spectral data were analyzed to quantify the levels of several radionuclides in a large population.[28] In this study a number of Fortran II programs for the IBM-7094 were used for the reduction of the pulse-height distribution data. The programs first performed a nonlinear least squares fit of a Gaussian function to the data points in the spectrum photopeaks. The associated Compton distribution required in the stripping program was then computed by interpolation from an experimentally-derived matrix of seven monoenergetic gamma rays originating in an appropriate phantom. Commencing with the highest energy, each designated photopeak and its associated Compton was subtracted off until the complex spectrum was analyzed. Use of programmed computers provides rapid and accurate quantitative interpretation of pulse-height distribution data, applicable to the determination of body burdens of various radionuclides.

Design Criteria for a Whole-Body Counting Installation in a Medical Center

In addition to the previously-mentioned requirements of the detector and its electronic components and its shielding, other general requirements must be met to provide a well-operated facility. Counters must be designed so that their operation can be integrated smoothly with existing facilities (generally a Research Hospital and OutPatient Clinic). Provision must be made to handle large numbers of patients with convenience and dispatch.

As an illustration of such a whole-body counting complex specifically designed for medical use, the plans of the proposed Brookhaven Medical Research Center's low-level counting facility are presented (Fig. 2). The building will encompass 5100 square feet and is to be constructed adjacent to the hospital of the Medical Research Center in such a location as to be convenient to the outpatient clinic as indicated. It will consist of five shielded counting rooms, together with unshielded reception, control, preparation and service function areas. The whole complex is to be provided with a self-contained recirculating air-conditioning and filtering system. This last requirement is of particular importance at Brookhaven due to the periodic contamination of the room with A^{41} from the large research reactor nearby.

Because of the extremely low background radiation requirements, the counting rooms will be heavily shielded with concrete walls and doors of 8″-thick steel. All interior surfaces of the counting room concrete

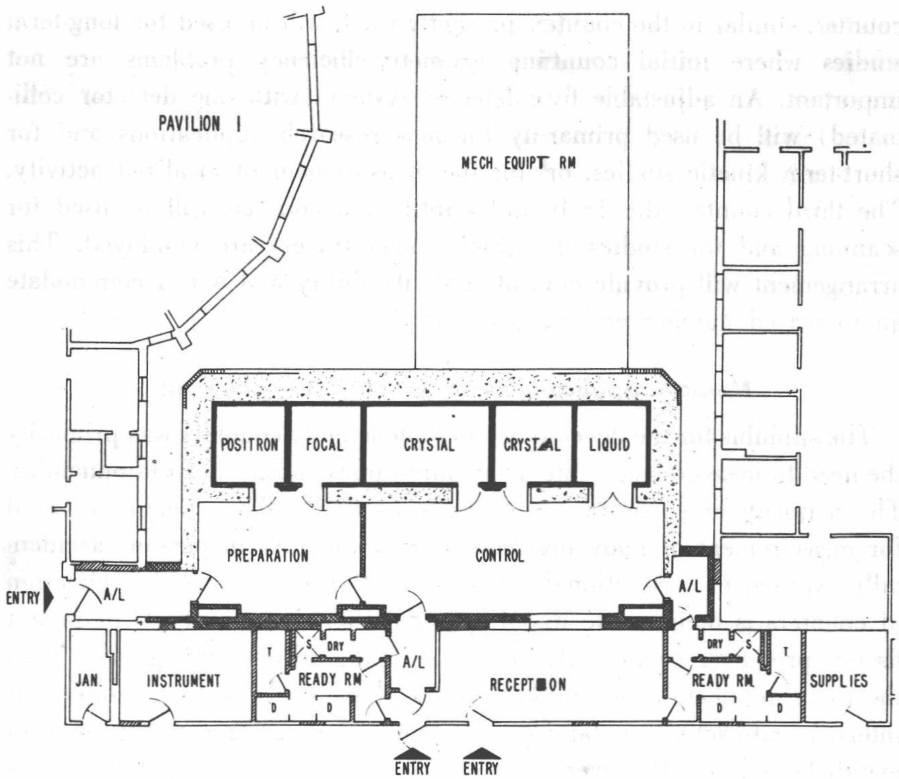

Fig. 2. Proposed plan for Brookhaven low-level counting facility.

shields will be lined with 4″-thick steel, ⅛″-thick sheet lead and 1″-thick plastic to shield the rooms from residual radioactivity in the concrete.

The Control Room will house instruments and control devices required for the operation of the counting equipment contained in three of the counting rooms. The Patient Preparation Room will provide space for the preparation of hospital patients and for instrumentation and control equipment for the other two shielded rooms. The Instrument Room will provide space to service electronic control and measuring equipment and to initiate the processing of the data. A Reception Room will be used to control the flow of patients through two Ready Rooms, which will contain dressing, toilet and shower facilities, to the Counting Rooms. Mechanical equipment space will be provided either in a basement, on grade adjacent to the building or in a second-story area.

The three different whole-body counters illustrated represent a very versatile arrangement for whole-body counting. A single crystal detector counter, similar to the counter presently used, will be used for long-term studies where initial counting geometry-efficiency problems are not important. An adjustable five-detector system (with one detector collimated) will be used primarily for new research applications and for short-term kinetic studies, or for the measurement of localized activity. The third counter, the 4π liquid scintillation counter, will be used for scanning and for studies in which single tracers are employed. This arrangement will provide considerable flexibility and will accommodate an increased number and range of studies.

Medical Applications of Whole-Body Counting

The stimulus for the development of whole-body counters was primarily the need to measure accidentally-acquired body burdens of radionuclides. The majority of apparatus in operation today (86 per cent) are used for measurement of body burdens of radionuclides in persons accidentally exposed in occupational situations.[1,2] A second general application of counters is their use to monitor populations for low levels of fallout fission products, particularly Cs^{137}, and naturally-occurring K^{40}. Thus the main application of whole-body counters has been as a monitor of internal radioactive contamination rather than as a research tool in metabolic studies. However, although it is used less extensively in this capacity, medical research is undoubtedly the most important application of whole-body counters.

Measurement of Absolute Levels of Radioactivity in Accidental Exposure.

Radium, Thorium, Uranium and Plutonium: The crystal scintillation whole-body counter was first used by Miller and Marinelli at Argonne in 1950 in a diagnostic application to determine body burdens of Ra^{226}.[29] Since that time a number of investigators have measured body burdens of Ra^{226} in persons contaminated in industrial situations or via medical therapy. [30-34] Ra^{226} clearance from the lungs following an inhalation exposure has also been measured by a crystal detector.[35]

The original crystal used for the Argonne Ra^{226} measurement was 1½″ in diameter and 2¼″ high, coupled to a single-channel analyzer. The room in which the measurement was made was lined with ¼″ of lead. From this simple set-up the spectrometric properties of sodium iodide crystal counters have been greatly improved by the development of various components of the system, such as 400-channel pulse-height analyzers, larger crystals and improved shielding to provide vastly increased accuracy and precision for measuring Ra^{226}. The object of these Ra^{226} studies is to correlate radium body burdens with the pathologic effects of chronic radiation. For the quantification of radium body burdens, gamma spectrometric analysis appears to be the best available technique.

It is of great importance that Ra body burdens be correlated with the resulting pathology, as these are the only data available which are sufficiently extensive to provide a basis for this correlation. Consequently, when it is necessary to estimate possible effects of body burdens of other radionuclides, they are referred to the Ra data. Our entire structure of estimated permissible body burdens of radionuclides rests on the Ra data, and it is therefore imperative that our best techniques be used to refine and make precise these primary data.

Another group of studies involving the determination of body burdens in patients is that concerned with Thorotrast ($Th^{232}O_2$).[36-41] The thousands of patients who received Thorotrast as a radiographic contrast medium 15 to 25 years ago constitute another unique population for the study of the long-term effects of chronic low-level radiation. In this demographic study it is necessary to correlate specific biological effects with the radiation dose from internally-deposited Thorotrast and its daughters. However, the body burden of Thorotrast, which locates itself primarily in the liver and spleen, is very difficult to assess. It appears that the problem may be amenable to solution by application of gamma-ray spectrometric analysis. Th^{232}, since it is an alpha emitter, can be determined by external measurement only indirectly from the gamma-ray abundances of its daughters. Gamma spectral data from patients have been obtained with an 8″ x 4″ sodium iodide crystal detector positioned over the liver.[41] However, because of the complexity of the decay chain of Th^{232} and differences in the metabolism of its various daughters, the analysis is difficult. The analysis of the gamma-ray spectra obtained by in vivo counting of Thorotrast patients was performed with the aid of an IBM-7094 computer program (Fig. 3). Determination of Th^{232} and its daughters here is equivalent to the measurement of seven different isotopes simultaneously. This study illustrates the excellent spectrometric capability of the sodium iodide crystal and emphasizes the necessity for computer analysis for complex problems.

The possibilities and limitations of whole-body counting of natural