The CLINICAL USE of RADIOACTIVE ISOTOPES

By

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PREFACE

THE modern history of scientific advancement is marked primarily by the close interrelationship of biology and physics, so that in the present view, certain biological phenomena are explicable only by an understanding of structure and function on an atomic and sub-atomic scale. An attempt to explain biological phenomena on the basis of the static condition of an organism, a tissue, or even a cell, at any given moment is to commit an anachronism as glaring as if one were to attempt to resolve all questions relating to the physical world on a philosophical or metaphysical basis.

Biological science in the twentieth century has progressed far beyond morphological description and analysis by the methods of classical chemistry, which characterized its earlier periods. It is no longer content to consider problems in absolute terms, but seeks rather to relate phenomena one to another The nineteenth century concept of the cell as the ultimate basic unit of all living matter has given way to a recognition of the atom as the true basis of all matter, living and non-living. Finally, it is now realized that increased knowledge of phenomena on a cosmic scale is to be gained only through increasing the accuracy of measurement and observation on the atomic scale.

Atoms in general may not be regarded as static structures composed of particles in fixed positions. Rather, they are dynamic entities changing in response to outside agencies affecting them, and in turn, being affected by them; and it is by examining the phenomena which occur during these changes that one obtains information concerning the structure of the atom as well as an insight into the nature of those qualities which produce or are the result of these changes. The atomic and molecular constituents of living bodies in particular are involved in an incessant flux of metabolic reaction. The inestimable importance to biological science of the discovery of artificial radioactivity lies in the fact that through this great achievement there have become available materials for the study of dynamic processes in which cell constituents are continuously involved. Through this means it has become possible to study normal biological processes minutely. There have also been added to clinical medicine new tools for diagnosis and for radiation therapy.

The present volume purports to acquaint the reader with the clinical applications which have so far been made of the available artificial radioactive isotopes. In fulfilling this task the author is not unmindful of the need for a fairly extensive knowledge of the physical basis of radioactivity to insure a complete understanding of the subject. Any exhaustive discussion of physics is omitted from the present work, however, since the literature in this field is abundant. The author urges the reader who wishes to go deeply into this field to have recourse to the volumes which are enumerated in the bibliography. For the reader who desires only such information as will enable him to follow the ensuing discussion with ease, the physical considerations are presented as briefly as possible, and in full recognition that they do little more than touch upon the underlying basis for the use of radioactive isotopes in clinical medicine.

This monograph has been written for the purpose of acquainting physicians and medical students with the physical principles of artificial radioactivity, and its uses in clinical medicine. The author's own experience in attempting to understand intricate problems of physics has prompted the use in this text of certain expressions such as "force of energy," "charged energy," etc., which are not in conformity with terminology accepted by physicists. Such liberties have been taken intentionally in an attempt to present complex physical processes in a more graphic way.

ACKNOWLEDGMENTS

THE completion of any book for publication leads the author very naturally to consider those factors which have played a part in enabling him to undertake and to carry through such a project. In the case of the present volume, much personal history is involved, and the reader's indulgence is asked for a brief recital of some of that history which has direct bearing upon the writing of a book about the clinical uses of radioactive isotopes.

In 1939, I accepted the invitation of Professor M. L. Oliphant of the Department of Physics at the University of Birmingham, to assist in the development of a program of medical use of radioactive isotopes—a field which was just beginning to capture the interest and imagination of leaders in many branches of science. The medical program which Professor Oliphant had envisioned had necessarily to be abandoned due to the imminent realities of World War II, but during a sixteen months stay in England, my own interest in the biological applications of artificial radioactivity became firmly based on a solid foundation to which Professor Oliphant's own wisdom and enthusiasm contributed both strength and durability. I am happy to have this opportunity of making grateful acknowledgment of that contribution.

In 1941, Dr. John H. Lawrence extended to me the privilege of joining the group of his associates at the Radiation Laboratory in Berkeley. The opportunity of observing and participating in medical activities with radioisotopes over a period of nearly a year, constituted an invaluable preparation for my subsequent work in this field of radiology. The warm relationship with Dr. Lawrence and the Radiation Laboratory which has continued since my transfer to the faculty of the Medical School in 1943, has been a source of much stimulation and assistance in my efforts to widen the scope of radioactive isotopes in medicine.

At the beginning of 1943, upon the recommendation of Dr. Robert S. Stone I was appointed to the faculty of the University of California Medical School and to the staff of the University Hospital in charge of radiation therapy. The period of my af-

filiation with the University of California has been rich in satisfactions, chief among which I count the friendly associations with my colleagues.

In the preparation of this volume many persons have contributed much valuable assistance and advice. While I wish at this time to express appreciation to all of those persons, the following must be singled out for special thanks:

Dr. Cornelius Tobias, Dr. Louis Strait, and Mr. Robert A. Blais read the parts of the manuscript concerned with physics and offered valuable constructive criticism. Dr. Kenneth G. Scott reviewed the entire manuscript and gave me the benefit of his long experience with radioactive isotope investigation. L. D. Marinelli, Dorothy Axelrod Heller, Drs. Robley D. Evans, Edith H. Quimby, E. H. Reinhard, E. R. Miller, K. G. Scott, Raymond P. Ghelardi, Cyril H. Brown, R. G. Fluherty and Titus C. Evans generously permitted reproduction of portions of their published work in this volume; the Isotope Division of the United States Atomic Energy Commission and Tracerlab of Boston have allowed use of material which has been published under their auspices.

Professor W. V. Mayneord has been especially helpful in making available to me some of his unpublished material relating to dosimetry; Drs. H. B. Jones, J. Gofman, and H. L. Dobson have furnished unpublished material on the preparation of radioactive chromic phosphate; Mr. Ralph Sweet advised regarding preparation of charts and tables, and Miss Joy Polis of Mr. Sweet's staff prepared some of the tables; Mrs. J. Mozley prepared the charts and figures with great skill, Miss Helen Wright assisted in the painstaking work of preparing the bibliography and index and Mrs. Shirley McSkimming typed and retyped the manuscript with accuracy, dispatch and great patience. Miss Mary Morrow edited the manuscript and assisted in its final preparation for publication.

Finally, but by no means last in importance and value, Dr. Milton Friedman offered helpful criticism and suggestions at all stages of writing the present volume, and Dr. Robert S. Stone has given generously both encouragement and support throughout the long period of its preparation.

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PHYSICS

Chapter I

THE PHYSICAL NATURE OF THE ATOM

THE almost infinite variety of chemical compounds encountered in nature includes relatively few (88) elementary substances. Each of these chemical elements is an aggregate of smaller units, **the atoms.**

The atom is the chemical unit of matter. Atoms are invisible by any mechanical device so far constructed, consequently visualization of an atom is a matter of concept.

CONSTITUENTS OF ATOMS AND THEIR PROPERTIES

A good working concept of the structure of the atom, based partly on mathematical considerations and partly on experimental evidence, was first propounded by E. Rutherford in 1911 and further developed by N. Bohr in 1913. The Rutherford-Bohr concept pictures the atom as consisting of a small, massive nucleus surrounded by a very light shell. The mass of an atom is concentrated to 99.98% in the nucleus. The atomic nucleus carries positive charges, the atomic shell negative charges. In a neutral atom the negative electrical charges of the shell balance the positive charges of the nucleus. A neutral atom is a dynamic system rather than a static structure composed of particles in fixed positions.

The electrons, which are the constituent particles of the atomic shell (Johnstone Stoney 1874, J. J. Thompson 1898), revolve about the nucleus at definite distances, many thousand times the diameter of the nucleus itself. The electron is a particle of matter and has a mass $Me = 9.106 \times 10^{-28}$ gms. The rest mass of the electron on the atomic weight scale, based on the number 16 for oxygen as the unit, is $A = 0.000548$. Each electron carries an elementary quantity of negative electric charge, called the electronic charge $e = -4.80 \times 10^{-10}$ electrostatic units.*

The nucleus of an atom is composed of protons (E. Rutherford, O. Lodge, 1920) and neutrons (Chadwick, 1932). The mass of the proton is $Mp = 1.65 \times 10^{-24}$ gm, that of the neutron is $Mn = 1.6622 \times 10^{-24}$ gm. Their mass "A" on the atomic weight scale based on 0^{16} differs slightly. A proton = 1.00761; A neutron = 1.00893. The atomic mass of a proton, and of a neutron, is approximately 1830 times greater than the mass of an electron. Each proton carries one positive electronic charge, $e = +4.80 \times 10^{-10}$ electrostatic units (e.s.u.). A neutron, as the name implies, is a neutral particle of matter without electrical charge. Therefore the neutrons contribute to the mass but not to the electric charge of an atom.

These three atomic constituents, the nuclear protons and neutrons, and the extranuclear orbital electrons, are elementary constituents of matter. The nature of each of these remains constant, irrespective of the atom in which it occurs.

SIZE OF ATOMS AND OF THEIR CONSTITUENT PARTICLES

Despite the extremely small rest mass of each of the atomic constituents, the space they occupy in forming an atom is rela-

* The unit quantity of electric charge, the electrostatic unit (e.s.u.) is that quantity of electricity which, if placed in a vacuum 1 cm distant from an equal and similarly charged quantity, will repel it with a force of 1 dyne. This definition was established by Coulomb in 1780, based on quantitative measurements of the mechanical forces an electrically charged body experiences. The definition is based on the principles of Newton's second law of motion with due regard for the magnitudes of Newtonian mechanics, and the means available for measurement of gross mechanical forces. The discovery of the atomicity of the electrical charge, followed by refinements in measuring devices introduced by J. J. Thompson, Ramsay, and Millikan led to the recognition that the quantity of electrical charge freely existing in nature is of the magnitude of around 4.8 ten billionth of the quantity defined by Coulomb as "the electrostatic unit." This elementary quantity of electric charge is referred to in modern physics as the "electronic charge" because it resulted from experimental studies concerning mass and charge of the electron. The electronic charge may be negative or positive. The negative electron, also called negatron, carries 1 negative electronic charge. One positive electronic charge is carried by the proton and by the positron which is a positive electron. Simple arithmetic shows that a total of 2,100,000,000 negatrons, or protons, or positrons carry the charge of *one electrostatic unit*. A larger unit frequently used in physics is

$$1 \text{ coulomb} = 3 \times 10^{9} \text{ e.s.u.}$$
$$1 \text{ coulomb} = 6.3 \times 10^{18} \text{ singly charged particles}$$