E. BRODA

Radioactive Isotopes in Biochemistry

RADIOACTIVE ISOTOPES IN BIOCHEMISTRY

by

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PREFACE

The use of isotopic tracers in biochemistry has grown from a very modest beginning to an immense structure in the course of 35 years. This development is quite remarkable, even in view of the fact that many branches of science have experienced extraordinary growth in the past few decades. The rapid development of biochemistry and the ready availability of labeled compounds have contributed largely to this result. The production of highly-active radioisotopes of most of the elements is made possible by the powerful beams of neutrons emerging from many present-day reactors. The chemist exhibits great skill in incorporating these radioactive tracers into a very large number of compounds—the catalog of Amersham (in England) alone contains 129 compounds labeled with ^{14}C.

The daily appearance of numerous biochemical studies employing radioactive tracers renders difficult the writing of a textbook on the use of radioisotopes. The author of the present book has found a happy solution to this problem. He adduces well-selected examples of problems which can only be solved by the use of radioactive tracers or whose solution is made appreciably easier by their use. Furthermore, he describes the techniques which are used in investigations with isotopic tracers. The fundamentals of radiochemistry, radiation chemistry, and radiation biology are also discussed.

When Wilhelm Ostwald was asked how he managed to turn out a large number of extensive volumes in a short span of years, he replied that his daughter stood at his left with blank sheets of paper, and his son at his right, taking away the finished sheets. In view of the fact that the author of the present work is now able to add to the books which have appeared in recent years this new and most successful one, one is tempted to believe that he has at his disposal some such system as that of Ostwald. He is to be congratulated on his performance.

G. DE HEVESY

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CHAPTER I

INTRODUCTION

1. Historical Survey

The importance of isotope methods in biology has frequently been compared with that of the microscope. Just as the invention of the microscope in the 17th century advanced the science of living tissues by tremendous strides, and made possible the later discovery of cells and microbes, so does the employment of isotopic methods put us in a position to investigate the details of metabolism in a reliable and highly sensitive manner.

The isotope—or tracer—technique originated at the Institut für Radiumforschung in Vienna, where G. Hevesy and F. Paneth carried out their classic researches shortly before the first World War. The first applications of the method were to the problems of inorganic and physical chemistry; solubilities of salts and rates of exchange of atoms between solids and solutions were determined. It seems astonishing in this era of speed that more than a decade elapsed before the new technique, so capable of producing results, was extended to a living system—once again, by Hevesy himself. The first biochemical application was an investigation of the uptake of lead by plants[1].

Even after the occurrence of the first biochemical investigation, progress was only halting. During the following years Hevesy and his coworkers published a few investigations on the metabolism of lead[2,3], bismuth[4] and thorium[3] in animals, and other authors, many of whom were directly influenced by Hevesy, undertook analogous experiments on lead[5–8], bismuth[9,10] and polonium[11–14]. Mention should also be made of the work on the distribution of radium in animals, which has been going on almost since the beginning of the century, but which is less biochemical than medical or toxicological[14–17] (*cf.* p. 145). Finally, some interesting investigations on the metabolism of the inert gas radon were published quite early[18–21].

A fast expansion of tracer techniques began only in the mid-thirties. This was caused principally by the discovery of the natural occurrence of the stable heavy hydrogen by Urey, the development of procedures for en-

riching stable isotopes, the construction of machines for transmutation by Cockcroft and Lawrence, and the discovery of artificial radioactivity by Joliot and I. Curie. These developments led almost immediately to an extension of isotopic methods from elements which have relatively little interest biologically, like lead, bismuth, thorium and radium, to the lighter elements which play predominant roles in the normal economy of living things.

Hevesy was the first to realize the importance of deuterium and of artificial radioisotopes for biochemistry. Two papers on heavy hydrogen appeared as early as 1934[22,23]; the heavy hydrogen was provided by Urey. (Pioneering work with heavy hydrogen was carried out in biochemical fields from 1935 onwards particularly by R. Schoenheimer, and brilliant successes were achieved[24]). There followed in 1935 a paper on 'Radioactive Tracers in the Study of Phosphorus Metabolism in the Rat'[25]. Nevertheless, a list of methods useful in the elucidation of reaction mechanisms compiled by a prominent biochemist as late as 1939 still failed to mention the isotopic method[26]. A general increase in the interest in isotopic methods came only after the second World War. This is attested briefly by Table 1 (below) which refers to the leading biochemical journals.

TABLE 1

FRACTION OF TOTAL NUMBER OF STUDIES PERFORMED WHICH USED LABELED ATOMS

Journal	*Volume and year*	*Radioactive isotopes* (%)	*Stable isotopes* (%)
J. Biol. Chem.	157 (1945)	1	4
(U.S.)	223 (1956)	39	7
Biochem. J.	39 (1945)	0	0
(Gt. Britain)	63 (1956)	18	1
Biochimia	11 (1946)	0	0
(Russia)	21 (1956)	7	1
Biochem. Z.	318 (1947/48)	0	0
(Germany)	328 (1956/57)	7	0

The most important point about isotopic methods is the possibility of distinction between atoms of the same element, that is, between the labeled and the unlabeled atoms. Hence it is possible to trace the movement (in the broadest sense) of the atoms in a system which already has a stationary concentration of atoms of the same chemical sort. Such an investigation is possible with no other method. Systems with stationary concentrations are obviously highly significant in biochemistry, and the investigation of metabolism in just such systems constitutes the central problem of biochemistry.

Stable isotopes are, in principle, capable of yielding the same results as radioactive isotopes. It is certainly technically more difficult to use them, but nevertheless it is necessary for those elements which have no suitable radioisotopes, especially nitrogen and oxygen[27]. Hydrogen and carbon can be labeled with stable or with radioactive atoms. No matter which isotope is used, the same results are obtained (disregarding the isotope effect; Chapter V). Even in the case of the latter two elements, however, the use of the radioactive labels is becoming increasingly frequent.

Stable isotopes of elements, which have useful radioactive isotopes, remain indispensable, or nearly so, only in three limited fields of application. (*1*) Because the concentrations of stable isotopes can be measured—with the mass spectrometer—more accurately than those of radioactive isotopes, they are often used for the determination of the isotope effect (Chapter V). (*2*) Because they can be employed in higher concentrations than radioactive isotopes, they permit the determination of reaction mechanisms by procedures in which all or nearly all of the molecules must be labeled (p. 42)[28]. (*3*) In certain experiments double labeling is necessary; in some such cases only a stable isotope can be used as the second label (p. 40).

Because of the qualifications of the author, the present book is devoted to radioactively labeled atoms, and does not discuss the techniques employed with stable isotopes. In the following, *radioactive* isotopes are meant when 'isotopic methods' are mentioned. Let us re-emphasize, however, that the majority of the results can in principle be obtained just as well with stable as with radioactive isotopes, so that a sharp distinction would be unnatural. Indeed, a not inconsiderable part of the investigations described in Chapters XI–XVI—especially the earlier ones—were carried out with stable isotopes.

2. Advantages and Limitations of Radioisotope Methods

There are several reasons for the preference given to radioactive isotopes. We note first of all the extreme sensitivity with which radioactive elements can be detected, permitting the observation of small numbers of atoms; hence work with radioelements can be carried out cheaply. Further, since the measurement of radioactivity is carried out by means of the external effects of the rays, the measurement is often performed on the intact system (non-destructive investigation). Finally, the determinations require relatively little time and effort, once the proper equipment has been obtained.

In comparison to these tremendous advantages of the radioisotope method, its single serious disadvantage, its low accuracy, is of slight im-

portance. Measurements of the intensity of radiation in biochemical practice rarely have an accuracy greater than 1–2%, since the sensitivity of the apparatus is subject to certain fluctuations and it is difficult to reproduce the positioning of the sample precisely. Radiochemical methods are therefore surpassed in accuracy by other chemical techniques. However, it is exactly in the biochemical field that—aside from the above-mentioned determination of the isotope effect—the requirement for extreme accuracy of individual determinations seldom arises. The biological variability makes any great precision seem pointless.

The application of the radioisotopic methods to biochemistry can also be called 'radiobiochemistry'. This term is derived from the concept of 'radiochemistry'. According to the fortunate definition of Paneth, radiochemistry is the chemistry of those substances which are detected by their (radioactive) radiations. The fundamentals of radiochemistry will be discussed in Chapter III.

Contrary to radiochemistry (Radiochemie, radiochimie, radiochimiya), radiation chemistry (Strahlenchemie, chimie des radiations, radiatsionnaya chimiya) is the science of the chemical effects of radioactive rays. Logically, then, one designates as radiation biology the important branch of investigation which deals systematically with the changes in living matter brought about by radiation, especially that from radioactive materials. The recommended nomenclature is then:

	In chemistry	*In biology*
Investigations with labeled atoms	radiochemistry	
Investigations of radiation effects	radiation chemistry	radiation biology

If a particular term for biological investigations with radioactive tracers is desired, the word radiobiology, analogous to radiochemistry and radiobiochemistry, suggests itself. Unfortunately, however, this term is sometimes employed as a synonym for radiation biology.

Within the compass of this book, therefore, radioactive atoms will be used as labels only, and the radiation emitted by them will be used for their analytical detection only. Hence, in this book it will always be tacitly assumed that the rays produce no disturbing effects in the materials investigated. Occasionally biochemists about to undertake work with radioisotopes entertain fear that this assumption may be unjustified. These fears are groundless when the work is properly carried out. Although one should remain aware of the theoretical possibility of such disturbances, one can in practice keep the amount of the radioelement, and hence the intensity of its radiation, below the level at which detectable

biological effects appear. The beginner in radiobiochemistry is herewith assured emphatically that a clean, sharp separation between this field and that of radiation biology is not only desirable, but easily possible. Some fundamental principles of radiation chemistry and radiation biology will be given in Chapters VI and VII.

Another problem of the isotope method lies in the possibility of isotope effects. It will be shown in Chapter V, however, that isotope effects can seriously disturb biochemical work only in the case of hydrogen. Even with this element there are ways and means of avoiding errors due to isotope effects (p. 40). In conclusion, therefore, it may be asserted that in practice the useful scope of isotopic methods is limited neither by radiation effects nor by isotope effects.

3. Plan of the Book

In view of the tremendous extent of contemporary biochemical work and the great portion of it which involves isotopic methods, it cannot be the purpose of our book to catalogue the most important results obtained by these methods. Moreover, a logical separation of the results of isotopic methods from those obtained by other methods in the same field of biochemistry would be impossible—witness, for example, the problems of photosynthesis.

For these reasons the author considers it his task to introduce the reader to the methodology of biochemical work with labeled atoms. After the principles of work with radioactive substances and of radiochemistry have been presented, the distinctive characteristics of the method will be discussed on the basis of suitable examples. The examples will be taken from the principal fields of biochemistry, and it will be left to the reader, if he specializes in a different sphere, to read for himself the literature concerning his own subject, or to decide how to adapt the procedures to his own field. Completeness in any direction will not be attempted.

A certain difficulty attends the attempt to draw a line between biochemistry and physiology. In this connection, we are guided by the words of Gowland Hopkins... 'What we have come to call General Physiology is now a rapidly advancing branch of experimental enquiry, and it is perhaps less easy to justify an attempt to distinguish between its activities and those of modern biochemistry than between the latter and those of classical physiology. There must be... an overlap in their fields which is entirely desirable. Yet there is still a distinction which seems to be real. Physiology as ordinarily understood is chiefly concerned in every case with the visible functioning of the organs; biochemistry rather with the molecular events which are associated with these visible activities'[29]. In

this book, too, some consideration of physiology is inevitable, but specifically medical questions will be avoided as much as possible.

A knowledge of the basic facts of radioactivity is taken for granted. It is presumed, therefore, that the reader is familiar with the concepts of radioactive disintegration, of α-, β-, and γ-rays, and of half-life. A number of elementary books are available to refresh the memory and broaden the knowledge of such matters[30–41].

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CHAPTER II

RADIOELEMENTS IN BIOCHEMISTRY

1. Natural and Artificial Radioisotopes

Because of their fundamental importance, and because of the confusion which exists with respect to them, it appears necessary at this point to define the concepts of 'activity' and 'intensity'. The (absolute) activity is the number of disintegrations in the sample per unit time. The activity has the dimension sec^{-1}. The activity thus defined is independent of the type or the energy of the emissions. For example, samples of radioactive hydrogen and radioactive phosphorus have the same activity if equal numbers of disintegrations take place in each in the same period of time, despite the fact that the average energy of each disintegration is one hundred times smaller in the first sample than in the second. The derived concepts of specific activity and relative activity will be introduced later.

The need for a general unit of activity has arisen. The activities of commercial radioelements, for example, must be expressed in definite absolute units. An activity of one curie (C) was originally ascribed to a source which underwent as many disintegrations per unit time as 1 g of radium (free of decay products)—approximately 3.7×10^{10} per second. This definition suffered from the fact that the activity of radium is not known very exactly. The curie has therefore recently been assigned a round value: one curie is exactly 3.7×10^{10} disintegrations per second. The activity of a gram of radium is therefore no longer exactly 1 C. One one-thousandth of a curie is a millicurie (mC), and one one-millionth is one microcurie (μC).

The number of rays striking unit surface per unit time is termed the intensity. The intensity is by this definition also independent of the type and energy of the individual emissions; its dimensions are $cm^{-2}\ sec^{-1}$. In practice the activity of a sample is usually measured by the intensity of its rays. This intensity is determined with the aid of a particular instrument located at a definite point.

Radioactive isotopes of all the chemical elements are known without exception. Several elements (Nos. 43, 61 and 84–101) exist only in the

form of radioactive isotopes. In some important cases, *e.g.* oxygen and nitrogen, all the radioisotopes are so short-lived that they are only of little use; the biochemist is fortunate, however, that the elements most important to him, hydrogen and carbon, possess isotopes with sufficiently long half-lives. A table of the radioisotopes most important for biochemical studies appears at the end of this book (Table 13, p. 324).

In some cases the naturally occuring radioelements are still employed today. For experiments with lead, bismuth, polonium, radium, francium, radon, actinium, thorium and uranium, for example, the natural isotopes are often employed. It is easy and cheap, for instance, to label lead for metabolic experiments either with long-lived radium D (lead 210; half-life $\tau = 19.4$ years) or with short-lived thorium B (lead 212; $\tau = 10.6$ h). The former is readily available in spent radon capsules from cancer hospitals, and the latter can be isolated easily and cleanly from thorium salts[1]. A general outline of chemical methods of separating the desired radioelements from accompanying materials will be given in Chapter III.

Much more important at the present time are the artificial radioisotopes. These are usually obtained by a reaction of slow neutrons with atoms. The atomic nuclei absorb slow neutrons better ('with a larger cross-section' as the physicists say) than fast neutrons. In most cases—but not in all—the slow neutrons are simply added to the atomic nuclei. The reaction is then designated as 'radiative neutron capture', or as a (n, γ)-reaction; a neutron enters the nucleus, and the binding energy is released as a γ-ray, or a cascade of γ-rays, without a particle being emitted. β-active isotopes of the original element are often produced by such neutron capture. For example:

$$^{23}_{11}\mathrm{Na} + {}^{1}_{0}\mathrm{n} = {}^{24}_{11}\mathrm{Na} + \gamma$$

or, in abbreviated form:

$$^{23}_{11}\mathrm{Na}\ (\mathrm{n}, \gamma)\ {}^{24}_{11}\mathrm{Na}\ \text{(instantaneous reaction)}$$

followed by:

$$^{24}_{11}\mathrm{Na} \xrightarrow{\beta} {}^{24}_{12}\mathrm{Mg}\ \text{(stable)};\ \tau = 15.0\ \mathrm{h}$$

A short-lived radioisotope is ^{128}I which is formed by bombardment of ordinary iodine with slow neutrons:

$$^{127}_{53}\mathrm{I}\ (\mathrm{n}, \gamma)\ {}^{128}_{53}\mathrm{I};\ {}^{128}_{53}\mathrm{I} \xrightarrow{\beta} {}^{128}_{54}\mathrm{Xe}\ \text{(stable)}$$

The half-life of this radioisotope is only 25 min, so that after 4 hours 99.9% of the radioiodine has disappeared. Very short-lived isotopes must be prepared at the place where they are to be used[2], and, of course, cannot be used at all for experiments of long duration.