Eight-year Isotope Summary

SELECTED REFERENCE MATERIAL

UNITED STATES ATOMIC ENERGY PROGRAM

Eight-year Isotope Summary

UNITED STATES OF AMERICA

VOLUME SEVEN

Eight-year Isotope Summary

UNITED STATES OF AMERICA

GENEVA: AUGUST 1955

SELECTED REFERENCE MATERIAL
ON ATOMIC ENERGY

VOLUME ONE Research Reactors
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VOLUME THREE Reactor Handbook: Engineering
VOLUME FOUR Reactor Handbook: Materials
VOLUME FIVE Neutron Cross Sections
VOLUME SIX Chemical Processing and Equipment
VOLUME SEVEN Eight-year Isotope Summary
VOLUME EIGHT Information Sources

Isotopes . . .

AN EIGHT-YEAR SUMMARY OF DISTRIBUTION AND UTILIZATION WITH BIBLIOGRAPHY

UNITED STATES ATOMIC ENERGY COMMISSION

March 1955

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Foreword

Interchange of scientific and technical knowledge will greatly facilitate the work of the scientists and engineers whose skills will be devoted to the future development of the peaceful uses of atomic energy.

The United States has made available to the world's scientific community a large body of such data. In honor of this historic Conference and to stimulate further exploration and development of the beneficial applications of nuclear energy, the United States Atomic Energy Commission has prepared this special collection of technical data for the use of the delegates and the nations represented.

The purpose of this collection is to provide information concerning the ways that we have found in which fissionable materials can be put to work in nuclear reactors for research purposes and for the production of power and radioisotopes.

It is our sincere hope that this material will be of practical value to the men and women of science and engineering in whose hands the great power of the atom is becoming a benign force for world peace.

Lewis L. Strauss

Chairman, U.S. Atomic Energy Commission

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INTRODUCTION

"Isotopes—An Eight-Year Summary of United States Distribution and Utilization" is a resume of isotope utilization during the first 8½ years of the United States Atomic Energy Commission's distribution program. It is also a supplement to the Three-Year and Five-Year reports of similar title issued by the Commission in 1949 and 1951. This report has been prepared to provide a source for quick reference to the many uses of isotopes and a bibliography on published work with them, categorized by fields of use.

At the cut-off date for the Five-Year Summary (June 30, 1951) the AEC had issued 13,103 authorizations (licenses) to procure isotopes; at the end of 1954, a total of 37,155 authorizations had been issued. During this period the number of United States firms and institutions using radioisotopes has increased from 622 to 2,416. Much of the increased growth has been in industrial utilization; the total number of industrial firms using isotopes increased from 134 to 1,020.

The number of published papers involving the use of isotopes increased from around 3,000 to more than 10,000. More than 7,000 recent open-literature references on work with radioactive and stable isotopes appear in Appendix V. Some special publications of interest to isotope users are listed in Appendix I.

Before the advent of the nuclear reactor, various radioisotopes were made through the use of cyclotrons and other sources of high-speed subatomic particles. They could, however, be produced only in minute quantities, at considerable cost. Although their importance as research tools was immediately recognized, they were available to only a few investigators. The discovery of nuclear fission changed the situation dramatically. The nuclear reactor, in which Uranium 235 is fissioned through a chain reaction process, is a source of radioisotopes in quantities millions of times greater than available previously, with a much greater variety of radiations, and at greatly reduced cost.

Radioisotopes of all the ordinarily stable elements can now be produced. So diversified and extensive have been the methods of artificially transforming atoms that is it now possible to make many more radioactive forms of atoms than the number of stable ones existing in nature. Only 270-odd stable forms, the stable isotopes of 81 of the elements, are known, whereas more than 900 radioactive forms of 100 elements have already been identified, most of which are made artificially.

Radiosiotopes are produced in a nuclear reactor by either of two processes. (1) The two parts into which a uranium atom splits, during the fission process, are radioisotopes of elements from atomic numbers 30 to 64, and can be chemically separated from the remaining uranium. (2) The neutrons, which are emitted when uranium fissions, are present in tremendous numbers and produce radioisotopes from materials inserted into the reactor.

After withdrawal from the reactor, the radioactive objects or materials can often be used directly as sources of radiation. In other cases, radioisotopes can be separated chemically from the irradiated material in concentrated form.

Early in 1946, the Manhattan Engineering District established an Isotopes Branch at Oak Ridge, Tennessee, to institute a distribution program.

The first announcement of radioisotopes available under the distribution program was published in the June 14, 1946 issue of *Science*. The first shipment, a small unit of Carbon 14, was made to the Barnard Free Skin and Cancer Hospital in St. Louis, Mo., on August 2, 1946.

A chronological outline of the development of the isotopes distribution program is given in Appendix II.

Less than 6 months following the start of the distribution program, the Atomic Energy Commission took over the administration of the atomic energy project from the Manhattan Engineering District. In a comparatively short time isotopes distribution became a well-established and growing program.

During the first year of the isotope distribution program, approximately 280 radioisotope shipments were made from Oak Ridge National Laboratory to 83 institutions which used them primarily in fundamental research problems.

At the end of 5 years, approximately 19,300 shipments had gone to over 600 institutions throughout the country, many of whom had begun using the material in applied research and routine applications. More than 2,700 shipments of concentrated stable isotopes had been made. In addition to the domestic distribution, some 1,100 radioisotope shipments had gone to approximately 250 institutions in 31 countries abroad.

During the first 5 years, Oak Ridge National Laboratory made all but a very few of the radioisotope shipments. Today, ORNL remains the primary source of supply but several other AEC Laboratories now distribute radioisotopes. In addition to ORNL, radioisotopes are produced at Argonne National Laboratory, Brookhaven National Laboratory, Mound Laboratory, the National Reactor Testing Station and Hanford Atomic Products Operation.

During 8½ years of distribution, more than 63,990 shipments have gone from ORNL to over 2,400 institutions throughout the country. United States users have received, in addition, more than 3,280 shipments of concentrated stable isotopes. At the close of 1954, 46 countries outside the United States had received 3,173 shipments of radioisotopes and 21 of concentrated stable isotopes at 659 institutions. Distribution of stable isotopes abroad was not begun until July 1954.

In the early days of the radioisotopes program individual shipments averaged about 30 millicuries. At the end of 5 years the average shipment was approximately 130 mc. Today the average shipment is more than 2,360 mc.

The sharp increase in quantity per shipment in part reflects commerial participation in the processing and redistribution of radioisotopes.

The total number of isotope shipments received by ultimate users is several times greater than the quoted number of shipments from ORNL. Many commercial firms purchase radioisotopes in bulk quantities and reprocess them into such forms as labeled compounds, certified pharmaceuticals, and custom-manufactured radiation devices; thus, a single large unit of radioactivity from ORNL may represent hundreds of shipments to individual licensed customers. In addition, thousands of shipments have comprised small license-exempt quantities of radioisotopes. Such license-exempt quantities are readily exchanged between institutions and are not included in the total shipments mentioned above.

More detailed data on growth of the distribution program are contained in Appendix III. Information is furnished on increased isotope shipments and curies shipped per isotope as well as per field of study in which the materials have been used.

Several nuclear reactors are now operating and many more will eventually be built. In reactors tremendous amounts of useful radioisotopes are produced as byproducts. These are truly a great peacetime byproduct—perhaps most important of the atomic age.

Principles of Isotope Utilization

RADIOISOTOPES

Radioisotopes are useful as sources of ionizing radiations and as tracer atoms. As sources of radiation, they are utilized in much the same way as radium and X-rays; as tracers, most of their uses are unique. The fundamental principles involved may be reduced to three major types or modes of use, as shown in Figure 1.

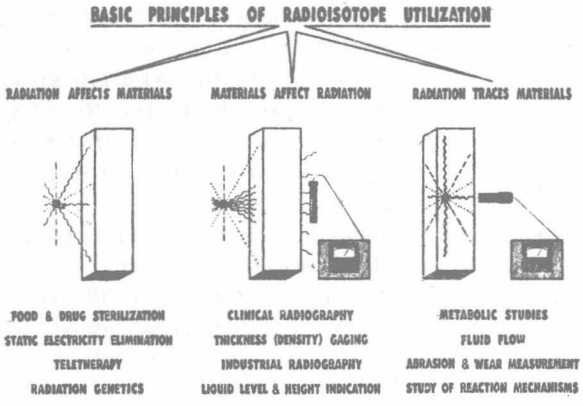

FIGURE 1.

Effect of Radiation on Materials.—In the first mode, the radioisotope is used simply as a fixed source of radiation much as radium and X-ray machines are used. There is a target material which is to be affected in some manner by the radiation. This material may be a cancer patient receiving radiation therapy, a plastic being irradiated to change its properties, or a bag of potatoes being irradiated to prevent decay; it may be the air surrounding a static eliminator or a phosphor incorporating a radioisotope which excites it to luminescence. The ability of radiation to alter a material is important in many ways.

Effect of Materials on Radiation.—In the second mode of use (fig. 1), the effect of the target material on the radiation furnishes information about the material. Here the application is based on measuring the radiation which penetrates or is reflected from the material. The radiation-detection device may be a counter or a photographic emulsion, depending on the application and type of information desired. This is the mode of use in medical radiography when a radioactive source replaces X-ray equipment. In industry it provides an ideal setup for testing purposes and is the basis for most radioisotope applications in product control. Examples of such applications include measuring the thickness of a moving sheet of metal, radiographing the internal structure of a piece of equipment or a casting, and measuring the liquid level in a closed container.

Tracing Atoms Through Their Radioactivity.—In the third mode of use (fig. 1), the radioisotope serves as a tracer to follow the complicated course of individual batches of atoms in physical transfer or chemical or biological reactions. To date this is the most important use of radioisotopes. Radioisotopes are incorporated into the materials of interest, rather than used as fixed sources of radiation physically removed from them. The radiosiotope used in a tracer serves as a tag or label which reveals the presence and identity of the material whether it is involved in a physical or mechanical transfer or in a chemical or biochemical reaction. The material labeled and traced may be water running through a pipe to an underground leak, sugar being utilized in a human being, a raw product for milk production in a cow's body, or an atom transferring from one kind of molecule to another in a chemical reaction.

Radiocompounds*

In many tracer studies isotopes must be incorporated directly into special complex compounds. For example, carbon, one of the major elements in plant and animal systems, is primarily of interest as part of a complex molecule

*The prefix "radio-", denoting radiation, was used by Marie Curie, in 1898, when coining "radioactivity". It has been extended to "radioisotope" and to radioactive elements (radiogold) and substances containing them (radiocompounds, radiocolloid).

such as an amino acid or carbohydrate. Radiocarbon, therefore, is often useful as a tracer only if it is first incorporated into the specific compound to be studied. In many instances it is also necessary to know the exact location of the radioisotope within the molecule, that is, to know which of the atoms within the molecule is labeled. The radioisotope will serve as a true tracer for a compound only as long as it remains part of the molecule. On the other hand, the same tracer atom can often be used to identify a second molecule formed from the first in a chemical sequence.

Isotope-labeled compounds may be prepared either by chemical or biological synthesis. To date nearly 1,000 labeled compounds are known to have been synthesized. Of these more than 500 have been synthesized by chemical means, that is, by procedures similar to those used in preparing the nonradioactive form of the same compound. Some complex labeled compounds which cannot be prepared by ordinary chemical procedures may be synthesized by the biochemical processes of animals and plants. Radioisotopes which have been injected into or fed to an animal may subsequently be extracted from the blood, urine, or tissues as part of complex organic compounds. Isotope-labeled compounds may similarly be extracted from plants.

Several hundred such compounds have been prepared by biological synthesis. The growth of isotope use, especially in the biological fields, will depend to an increasing extent on the availability of a wide variety of labeled compounds.

Detection of Radiation

The useful radiations from radioisotopes are mainly of four types: (1) Alpha particles, identical with the nucleus of a helium atom, are emitted chiefly by isotopes of the heavier elements. They produce intense ionization but have very little penetrating power. (2) Beta particles, identical with negative electrons, have less ionizing power than alpha particles but are much more penetrating. (3) Gamma rays are highly penetrating electromagnetic radiation and do most of their ionizing by means of high-speed electrons they eject from atoms. X-rays are emitted from atoms by a different process but are otherwise identical with gamma rays of the same energy. (4) Positrons are similar to beta particles and have similar ionizing power but are positively charged. They are encountered less frequently than the other types of radiation.

These radiations are detected through their effects on material. Radiation which passes through a material disrupts many of the molecules, producing positively and negatively charged fragments called ions. This ionization is revealed by either the electrical effects or recombination effects of the ions.

The radiations are most commonly detected and counted with sensitive electronic instruments such as geiger counters or scintillation counters. When a particle of radiation enters a geiger counter, it ionizes a gas and thus triggers an electrical discharge. The resulting tiny current is amplified to produce a signal seen, heard, or mechanically counted.

In a scintillation counter, the particle produces a minute flash of light in a liquid or crystal as the disrupted molecules give off energy in recombining. A light-sensitive device converts the flash to a tiny current which is then amplified.

Sensitivity and Specificity of Radoisotopes

Radioisotopes permit materials to be traced in minute quantities—a millionth to a hundred-millionth of the amount detectable by other means. It is easy to detect radiation from isotopes diluted with a billion or 10 billion times as much nonradioactive material. Some isotopes are still detectable after dilutions of more than a trillion.

This means that it would be possible to detect one hundred-millionth of an ounce of radioactive material dispersed, for example, in a 1,000 pound cow.

Even more important than sensitivity is the specificity of radioactive tracer atoms. They can label a specific batch of atoms and enable it to be traced through a series of chemical or physical processes. The labeled atoms can be traced in spite of multiple reactions with numerous other atoms or molecules. This permits the sorting out and untangling of complicated processes which can be followed in no other way. Tracer atoms are, therefore, unequaled

for studying complex chemical or biological processes.

The sensitivity of radioisotope detection, the specificity of the tracer method, and the unique radiation characteristics of individual radioactive species, permit radioisotopes to be used as powerful analytical tools in at least three major ways. These may be referred to as "tracer analysis," "isotope dilution analysis," and "activation analysis."

Radioisotopes as Analytical Tools

Tracer analysis constitutes perhaps the simplest type of tracer application. It is designed to follow the fate of a radioelement or radiomaterial from one stage to another of a reaction or a process. It is primarily useful in determining the distribution of a specified material in a variety of end products. The techniques may be either qualitative or quantitative. They can give information as to "what, when, and how" or can tell "how much." In either case, the advantage is that the determinations can be made at a concentration far below those permitted by other methods. The analysis frequently involves chemical separation of the material at a chosen stage of the process. Measurement is then made of the radioactivity in the different separated fractions.

Isotope dilution analysis is a modification of tracer analysis. It is particularly suited for determining the amount of a substance which is present in a process or system at a concentration too low to be measured by chemical or other methods or which cannot be separated from the other materials for separate measurement. The technique is based on putting into the system a small, known amount of radioactive (labeled) substance similar to the unlabeled substance to be measured.

After a period of mixing, the ratio between labeled and unlabeled substance is the same throughout the system and can be measured with a counter in a sample withdrawn for test purposes. The amount originally in the system can then be computed from its ratio to the known amount added.

An isotope dilution analysis can be likened to a method used by some investigators for estimating the number of fish of a certain kind in a pond. One hundred catfish, for example, can be released into the pond with clipped tails as labels. After sufficient time for thorough mixing of the fish, a sample can be taken with a net. If 100 catfish are removed, 10 of which are marked, it can be assumed that the catfish have been diluted to a ratio of 10 to 90, or 100 labeled to 900 unlabeled. Thus there were 900 catfish already in the pond.

Activation analysis can be used to identify and measure an unknown element in a sample or to determine the concentration of an element known to be in the sample. This is accomplished by exposing the sample to neutrons, as in a nuclear reactor. Some of the atoms of each element present are made radioactive, and those with suitable radiation characteristics can be identified. The technique can either be qualitative or quantitative. It is particularly useful when the concentration of an unknown element is too low to be identified by chemical or spectroscopic methods or where standard methods of analysis are not satisfactory because of interfering contaminants. Examples of applications suited to activation analysis include the determination of minor elements in animal tissue, garden products, and minerals.

STABLE ISOTOPES

Stable isotopes are also valuable as tracers, and their use has led to many important scientific discoveries. Most elements have one or more stable isotopes, which exist in fixed proportions in the element as found in nature. The natural proportions may be changed by increasing the relative abundance of one of the isotopes in a sample of the element. Such a concentrated stable isotope can be followed in a system by taking samples and observing the changes produced in the relative abundance of the isotope as normally found in the system. The isotope's abundance is determined with a mass spectrometer, which sorts out the isotopes of various weights. This method of tracing

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atoms is valuable and has found considerable use, but it is not as versatile or as sensitive as the use of radioactive tracers.

Radioactive and stable isotopes have proved especially beneficial in medical and biological research, medical diagnosis, medical therapy, agricultural studies, chemical and physical research, and industrial applications. Their usefulness in each of these broad fields is discussed in the following sections.

Medical and Biological Research

No other field has benefited as profoundly from the ready availability of radioisotopes as the life sciences. As tracer atoms these new tools are so uniquely suitable to solution of problems in this field that they seem almost to have been created for the purpose. Body processes, in sickness and in health, are fundamentally chemical but are carried out on such a dynamic, complex, and microscopic scale that they frequently defy ordinary chemical procedures in their study. Even the sensitive techniques of microchemistry are often too crude and slow to analyze biological processes.

Tracers of various kinds were used in biological studies before the advent of radioisotopes. Dyes can be used in some cases to follow a material and reveal its presence. Peculiar groups of atoms can be joined to molecules of a compound to identify it in later chemical tests Such tracers can follow dynamic processes but have two important defects: (1) they are different from the material they trace so that there is no assurance they follow the same chemical pathways and (2) where the traced material is greatly diluted during a process, so much of "foreign" tracer must be used that it affects the process itself.

The reason for supremacy of radioactive tracers is thus apparent. They correspond in size and kind to the things they trace. They are not foreign or chemically different. Indeed, they are not *added* to a material—they *are* the material or a true part of it. A molecule of vitamin B–12 is exactly that compound whether it has its cobalt atom in a stable or in a radioactive form, and the body treats it exactly the same. Radioisotopes, therefore, are "natural" tracers and, as far as biological processes are concerned, are no different from other atoms except in their ability to send out signals to identify their presence. These signals are the radiations which can be detected by instruments as previously mentioned.

Except for the important elements oxygen and nitrogen, useful radioactive forms are now available for most elements which enter into biological processes. Sodium, for example, is important in body fluids and tissues and is easily traced by means of its radioisotope, Sodium 24. In one type of application, illustrated in Figure 2, a solution of common salt, or sodium chloride, is labeled with this isotope and injected intravenously. Transfer of sodium to various body sites is then traced and measured by means of the Sodium 24 gamma rays.

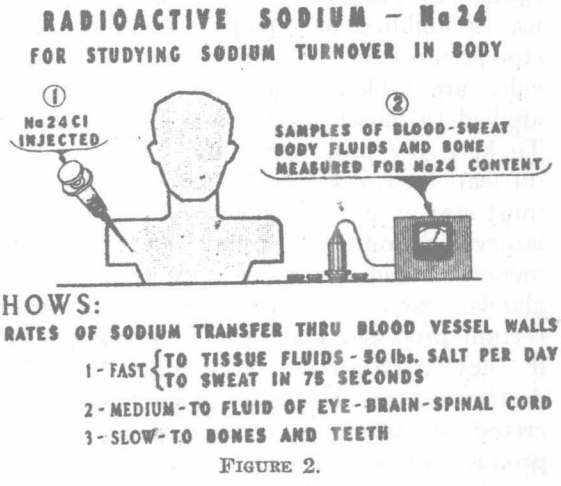

FIGURE 2.

The speed of this transfer and incorporation into body compounds well illustrates the extremely dynamic quality of life processes. Only a few seconds are required for the blood stream to carry the sodium from one arm, through the heart and lungs, and into the other arm. In another type of study, the conversion of injected radiocarbon-labeled acetate into labeled carbon dioxide is found to start almost immediately. The radioactivity in the exhaled breath reaches a peak in about 15 minutes.

Often it is necessary to trace a certain kind of molecule or part of a molecule rather than particular atoms. To meet this need, a growing assortment of hundreds of organic molecules have been provided with radioactive replacements for one or more of their atoms. These tracer compounds, purchased from commercial processers or synthesized by the researcher himself, include such materials as proteins, sugars, amino acids, vitamins, and hormones. With so varied an array of research tools at his

command it is not surprising that the biologist has been able to find answers to many perplexing problems of his science. For many of these problems, radioisotopes provide the first key to a solution.

If the human body were always perfectly healthy, interest in its intricacies would be academic. But, because things go wrong with its structure and processes, it becomes of prime importance to know all that can be learned about it. The body is an exceedingly busy chemical laboratory. It is continuously processing raw material into products suitable for use in building or repairing its parts, or for storage until they will be needed. Food molecules are broken down and their energy is applied to muscle action and other functions. To keep the processes running efficiently, an intricate control system of checks and balances must stay in good working order. This regulatory function is performed primarily by hormones secreted into the blood stream by various glands. Some hormones increase the rate of certain processes and others counteract them if they overcontrol. Still other substances destroy certain hormones if too much is secreted, or stimulate certain glands to overproduce when necessary. Not only rates of reactions but also such things as body temperatures, fluid pressures, and chemical concentrations must be kept within very narrow limits.

In view of this complexity and the many possible changes produced by disease or accident, the need for intense study is immediately apparent. To recognize, understand, and treat abnormal conditions, medical men need to know what is normal, to understand details of processes in the healthy body. Some are so complex that only through radioisotope tracers has any success in unraveling them been achieved.

The cells of the body themselves are the "test tubes" in which most of the chemical processes are carried out. The work of recent years has made this fact clear and much of the research is now being done at the cellular level. Three main subjects are being pursued in this work: (1) the fate of normal metabolites, (2) the action of drugs, and (3) the action of injurious agents.

FATE OF NORMAL METABOLITES

Isotope tracer techniques are being widely employed in studies of the normal chemical activities, or metabolism, of the body. Metabolites, those substances which are essential to these processes or are produced by them, are being labeled and then traced by various techniques.

Calcium Metabolism

Of the 92 natural elements, 15 or 20 are known to be essential to life processes. Most of these have been used in tracer studies designed to show their normal metabolism in the body. For example, radiotracer studies showed that nearly 90 percent of injected calcium concentrated in the bones of young animals; in the old the bone uptake was about 40 percent. Dietary factors have been found which reduce the amount of calcium available to the body. This action may possibly be of value in treating certain diseases. Even more effective is the compound ethylenediaminetetraacetic acid, which has a great affinity for the calcium and tends to remove it from the body.

Protein Metabolism

A large part of the work with metabolites is motivated by the hope of cancer control. If differences can be found between the needs of cancer cells and those of normal tissue it may be possible to retard or prevent the growth of one without seriously affecting the other.

Protein metabolism, because of its fundamental role in life processes, is receiving the greatest share of attention. In a typical study, the essential compound glycine was labeled with Carbon 14 and injected into normal rats and rats with liver tumors. The rats were then sacrificed after various intervals of time so that metabolism was stopped at various stages of completion. The tumors and normal liver tissue in each case were then broken down chemically and the many intermediate compounds, the amino acids which lead to the eventual building of body protein, were separated. The radioactivity of each fraction was measured; any activity demonstrated that the particular

fraction contained parts of the original glycine molecules. From the way in which the C–14 activities varied from one stage of completion to another the experimenters could draw up a "flow scheme" of glycine metabolism. As in almost all such metabolism studies, the same general scheme was found in both normal and cancer tissue although significant differences occurred in the relative importance of some of the steps.

Nucleic Acid Metabolism

Nucleic acid-protein combinations, the nucleoprotein molecules, are the essential material of cell nuclei, including the chromosomes. Nucleic acids, therefore, are fundamental to the life of the cell and to heredity, and the step-by-step processes in their production have received as much attention as those in the case of protein. In general, the same types of tracer techniques are applied to the two; these will be discussed further in relation to anti-metabolite drug action.

Citric Acid Cycle

Tracer techniques have also been used in studies of the citric acid cycle. This cycle, a normal part of cell chemistry, was formerly thought to be missing in malignant cells. However, since C–14-labeled carbon dioxide was found to be given off and citric acid to be produced by such cells when fed C–14-labeled carbohydrates and fatty acids, it was proved to occur in them also.

Hormone Metabolism

Radioactive tagging of various hormones which are known to play an important role in the body has contributed greatly to their understanding. Since a small injected quantity mixes with the same substance produced by the glands, it is possible to find how the body treats its own regulators. In the system of checks and balances, mentioned earlier, the hormones stimulate various chemical processes but, at least in some cases, are continually being destroyed by enzymes which control their amount. Enzymes may, in turn, be controlled in their action by other interfering substances.

The mechanism by which the body controls the insulin hormone is being studied with Iodine 131-labeled insulin. An enzyme-like system in the body, called insulinase, breaks down the insulin molecule. By injecting labeled insulin into mice and then measuring the radioactivity of the breakdown products in their livers, it was found that 1 percent of the insulin is destroyed every 2 minutes during at least the first 2 hours. This destruction must evidently be taken into account in any consideration of diabetes control.

Further study has shown that the liver contains an insulinase inhibitor, an enzyme antagonist, which reduces the destruction by about 78 percent when injected a half-hour before the insulin. Thus, it seems that a balance is normally maintained between the production of insulin and its controlled destruction. If production is low or destruction too rapid, the supply of insulin drops and a diabetic condition develops. The insulinase inhibitor tends to maintain the supply, but whether this substance will be effective as a treatment in diabetes must be determined by clinical trials.

Insulin is necessary in the metabolism of glucose, the form in which most food is absorbed into the blood stream after digestion. Without it the final step of converting sugar to energy or stored fat does not take place. The exact site of the insulin action has not been determined but recent studies with radiocarbon suggest that the hormone helps to transfer glucose through the cell walls and into the cell where it is actually used.

Information is gained in this particular line of research both by labeling insulin and by labeling substances it acts upon. Radioisotopes provide a two-way tool in this respect and permit very effective dual attacks on many similar problems in cause and effect.

A rapid method for measuring pepsin activity in the digestive system would be of benefit to clinical studies of this enzyme in pernicious anemia and cases of gastric ulcer. The breakdown of serum albumin by pepsin, during digestion, produces certain products which can be chemically separated after excretion. After an oral tracer dose of C–14-labeled serum, the