USES OF RADIO-ISOTOPES. 2-CLINICAL USES OF CERTAIN RADIO-ISOTOPES*

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Post-war developments of tracer techniques have paved the way for a newer conception of the difficult problems of biological researches, crumbling the old viewpoints to pieces.

Three main problems arise while studying the detailed metabolic process in the organism. (1) Identification of the usual nutrients and metabolites required by the system; (2) Investigation of the pathways by which metabolites are incorporated, utilised and dissimilated by the cells; and (3) Elucidation of the functions of the specific cells, specially in relation to the requirements and functions of the whole organism.

The two experimental variables are the organism and its metabolites. We can study either the normal system supplied with unusual types of metabolites or the abnormal system supplied with the usual metabolites.

The radio-isotopes have extensively provided a tool of comparable importance to chromatography in the study of complex metabolic changes taking place in the living cells and in the problems of intermediary metabolism and synthesis which had long appeared insoluble. For any particular nutrient or factor, the broad paths of complete metabolism are first mapped out from the study of the whole organism; then these paths are separated into sequences and steps of intermediate metabolism by different techniques. Since isotopic atoms cannot be distinguished biologically except by physical means, it is reasonably assumed that the metabolic pathways of compounds differing only in their isotopic composition are identical, and also that the radiation from radio-isotopes do not itself alter the metabolic systems, provided only a "tracer dose" of isotope is used.

When an isotope is added to a biological system, it may or may not be incorporated into the system under study. Although the system may contain the same element or compound as the introduced material, the labelled atoms are distinguishable because of their physical properties, and the movement of these particular atoms can be followed as they pass from one molecular form to another, as though the tracer atom was visible to the experimental biochemist throughout its passage from intake to excretion. This following up of the metabolic wanderings has also brilliantly overcome various objections which are put forward against other techniques.

After entering a biological system an isotope is continuously diluted into the pool of stable elements or compounds. Even though the specific activity (radioactivity per unit weight of radioactive material) may be

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reduced several fold by this process of dilution, the isotope is usually still readily detectable until it is diluted below the sensitivity of the detecting instruments. Simultaneous use of distinguishable isotopes of the same element or of two labelled atoms in the same compound gives better information.\textsuperscript{5} By analysis it is possible to obtain information about the rates and the various intermediate steps in the metabolism of the labelled compound.

Many of the important biochemical studies with C\textsuperscript{14} in the intact human subjects can be made by the use of a few hundred microcuries, or a less certain diagnostic study can be performed with only a few microcuries. For instance, injected glucose with tagged C\textsuperscript{14} mixes with the glucose of the blood and extra-cellular fluid. Then it reaches the active enzyme sites within the cells, which involves the transport across the cell-membrane. It then enters the metabolic cycle which involves a series of enzymes and intermediate compounds. Thus, although the chemical state remains in equilibrium, the dynamic properties of a system can be revealed.

Labelled amino-acids have been largely used either to study the metabolic behaviour of amino-acids themselves or to observe the appearance of labelled proteins and, in turn, to study their behaviour—a matter of great interest to the clinicians. Within the cells in which protein synthesis is in progress, it appears that the assembly of a complete set of amino-acids in a single operation is involved. Thus, when several labelled amino-acids are presented to a cell, the new protein molecules of different kinds which are produced contain these amino-acids in a specific activity relationship which must be that of the free intracellular amino-acids. The labelled protein molecules appear in many parts of the body such as the intestinal mucosa, kidney, liver, plasma, spleen, etc. following the oral or parenteral administration of isotopic amino-acids. Many of the details of the metabolism of carbohydrates, fats and proteins have been obtained by isotopic tracer studies, e.g., (1) the breakdown and synthesis of fatty acids, (2) the rate of tissue assimilation of glucose, (3) the transformation of sulfa-containing aminoacids, (4) the transmethylation reaction, (5) the transaminase reaction (6) urea synthesis, etc.

Formerly food was considered as a fuel used for supplying the energy or for repairing the wastage of the tissues. Pioneering works of \textsc{Schoenheimer} and others with radio-isotopes have shown beyond doubt that "the biological reactions"; i.e., the majority of the components of a living system are in a state of dynamic equilibrium—in a state of balance between breakdown and resynthesis; that the products derived from tissue breakdown are chemically and metabolically indistinguishable from many of the materials obtained directly from the external environments, e.g., food, and the classical distinction between exogenous and endogenous metabolism disappears; that the complex materials of living systems are built up from the small specific precursor molecules of the metabolic pools.

As a result of these types of investigations it has been realised that many simple substances, such as acetate, carbon dioxide, glycine and related compounds have great importance in biologic economy.