QUARTERLY REVIEWS

THE PREPARATION OF RADIOACTIVE TRACERS *

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SHORTLY after the discovery that some radioactive elements were practically inseparable from well-known inactive elements, their use as " indicators " was recommended. Although in those days the number of suitable radioactive elements was small and, moreover, limited to the last two rows in the Periodic Table, they proved to be a great help in a variety of investigations in inorganic and physical chemistry. It was, however, only after the artificial production of radioactive isotopes of the lighter elements had been discovered, that the method attracted the interest also of biologists and medical research workers.

In view of the extensive use now made of radioactive " tracers " in biological and non-biological sciences, the question of their preparation assumes an ever-growing importance. For many problems more than one tracer substance can be advantageously applied, and many tracer substances can be obtained in more than one way. To deal with the whole wealth of information published during the last few years would require a volume. We shall confine ourselves here to a description of the principles underlying the preparation of radioactive tracers, and illustrate them by a few examples.

Generally four stages can be distinguished whenever a radioactive tracer is prepared. (I) The selection of a suitable tracer substance. (II) The production of the chosen radioactive atoms. (III) The analytical separation and concentration of these atoms. (IV) The synthesis of the tracer substance incorporating the radioactive atoms. We shall deal with each of these stages in turn.

(I) *Selection of a Suitable Tracer Substance*

The choice of the tracer substance has, of course, to be made by the worker who is going to use it ; but he should be acquainted with the points of view of the physicists and chemists who will be responsible for the stages II, and III and IV, respectively.

In the interest of his own work he will try to obtain for his tracer substance

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an isotope—or what is better called, a " nuclide "[1]—which emits sufficiently energetic rays to make the quantitative measurements easy, and which has a convenient half-life. It is obvious that too short a life tends to make the experiments difficult or impossible ; but also too slow a disintegration rate may be unwelcome, *e.g.*, if the tracer is to be used in biological experiments where the introduction of a permanent radioactivity into the organism may have to be avoided. Moreover, it follows from the disintegration laws that the time needed for attaining the necessary activity of a long-lived artificial radio-element may be prohibitively long.

In Table I we have brought together the radioactive nuclides with their half-lives which seem to be the most useful ones for tracer work. (For the meaning of the asterisks, see p. 105.)

TABLE I

Element.	Isotope.	Half-life.	Element.	Isotope.	Half-life.	Element.	Isotope.	Half-life.
1	^{3}H	31 y.	30	* ^{65}Zn	250 d.	52	^{129}Te	32 d.
6	^{11}C	20·5 m.		* ^{69}Zn	13·8 h.	53	* ^{131}I	8 d.
	* ^{14}C	5100 y.	33	^{74}As	16 d.	54	^{135}Xe	9·4 h.
9	^{18}F	2 h.		* ^{76}As	26·8 h.	55	^{137}Cs	33 y.
11	^{22}Na	3·0 y.		* ^{77}As	40 h.	56	^{131}Ba	12 d.
	* ^{24}Na	14·8 h.	34	^{75}Se	125 d.	57	^{140}La	40 h.
14	^{31}Si	170 m.	35	* ^{82}Br	34 h.	58	^{141}Ce	30 d.
15	* ^{32}P	14·3 d.	36	^{85}Kr	4·5 h.	59	^{142}Pr	19·3 d.
16	* ^{35}S	87·1 d.	37	^{86}Rb	19·5 d.	63	^{154}Eu	5–8 y.
17	* ^{36}Cl	10^{6} y.	38	* ^{89}Sr	55 d.	73	^{182}Ta	97 d.
	^{38}Cl	37 m.	39	^{90}Y	65 h.	74	^{185}W	77 d.
18	* ^{37}A	34 d.	40	^{95}Zr	63 d.	75	^{186}Re	90 h.
19	* ^{42}K	12·4 h.	41	^{95}Nb	36 d.	77	^{192}Ir	70 d.
20	* ^{45}Ca	180 d.	42	^{99}Mo	67 h.	79	* ^{198}Au	2·7 d.
21	^{46}Sc	85 d.	43	^{99}Tc	10^{6} y.		* ^{199}Au	3·3 d.
22	^{51}Ti	72 d.	44	^{103}Ru	42 d.	80	* ^{197}Hg	64 h.
24	^{51}Cr	26·5 d.		^{106}Ru	1 y.		* ^{203}Hg	51·5 d.
25	^{54}Mn	310 d.	46	^{103}Pd	17 d.	81	^{206}Tl	3·5 y.
26	* ^{55}Fe	4 y.	47	* ^{110}Ag	225 d.	83	^{210}Bi	5 d.
	* ^{59}Fe	44 d.		* ^{111}Ag	7·5 d.	84	^{210}Po	140 d.
27	* ^{60}Co	5·3 y.	49	^{114}In	48 d.	85	^{211}At	7·5 h.
28	^{59}Ni	15 y.	51	* ^{122}Sb	2·8 d.	93	^{239}Np	2·3 d.
29	* ^{64}Cu	12·8 h.		* ^{124}Sb	60 d.	94	^{238}Pu	50 y.
				* ^{125}Sb	2·7 y.			

Only artificial radio-elements are included in the above table. In rarer cases, however, some of the natural radioactive substances may be helpful in tracer experiments, and we give, therefore, in Table II, a list of those most likely to be employed.

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[1] In the literature on radioactivity, it has recently become customary to refer to the seven hundred odd atomic species of the 96 known elements as " isotopes ", thus neglecting the original meaning of the word which designated the atomic species of one and the same element which occupy " the same place " in the Periodic Table. To-day, as well as thirty years ago when F. Soddy coined it, we need a word for describing this special relationship of two atomic species, so we agree with T. P. Kohman (*Amer. J. Physics*, 1947, **15**, 356) that this loose usage of the term isotopes is to be discouraged ; and since the expression " atomic species " is awkwardly long, we adopt here the new word " nuclide " introduced by Kohman.

TABLE II

Element.		Isotope.	Half-life.
81	Thallium . . .	Thorium-C″	3·1 m.
82	Lead	Radium-D	22 y.
		Thorium-B	10·6 h.
83	Bismuth . . .	Radium-E	5·0 d.
		Thorium-C	60·5 m.
84	Polonium . . .	Polonium	140 d.
86	Emanation . .	Radon	3·82 d.
87	Francium . . .	Actinium-K	21 m.
88	Radium . . .	Radium	1590 y.
		Thorium-X	3·64 d.
89	Actinium . . .	Actinium	13·5 y.
		Mesothorium-2	6·13 h.
90	Thorium . . .	Radiothorium	1·9 y.
		Uranium-X	24·5 d.
91	Protoactinium .	Protoactinium	$3{\cdot}2 \times 10^4$ y.
		Uranium-Z	6·7 h.

The preparation of these natural radio-elements has been fully described in a fairly recent publication by O. Hahn,[2] to which not much new could be added, and we shall, therefore, not deal with this matter in the present survey. Examples of the application of natural radio-elements as tracers can be found in the same book and in earlier works.[3]

Some investigations, especially those of a biological nature, often require tracers of negligible weight because the incorporation of any appreciable amount of matter would create non-physiological conditions. The demand for a high " specific activity " * of the tracer is likely to increase the difficulties of its production.

Sometimes an otherwise suitable nuclide may not make a convenient tracer because of complications in its assaying arising from the activity of its disintegration products ; in other cases, however, the measurement may be facilitated by the stronger radiation of a daughter substance which quickly reaches radioactive equilibrium with the tracer.

(II) *Production of the Tracer Nuclides*

There are many processes known for the creation of artificial radio-elements ; the following are of principal importance in tracer production : [4]

(A) Bombardment of stable atoms with neutrons.

(B) Bombardment of stable atoms with deuterons.

(C) Splitting of uranium into active nuclides.

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[2] " Applied Radioactivity ", Cornell University Press (New York, 1936).

[3] F. A. Paneth, " Radioelements as Indicators ", McGraw-Hill Book Company (New York, 1928).

[4] In special cases also the bombardment with α-particles proved to be a useful method (J. G. Hamilton, not yet published) ; *e.g.*, ^{42}K, free from ordinary potassium, can be obtained by irradiating argon with α-particles of high energy, according to the equation $^{39}_{18}A + ^{4}_{2}He \rightarrow ^{42}_{19}K + ^{1}_{1}H$.

* By specific activity we understand the number of disintegrations per second, per gram of the tracer substance.

Process A can be carried out in three different ways : with a radium–beryllium source, with a cyclotron, and in a uranium pile, while B is restricted mainly to the cyclotron, and C to the pile.

(A) *Neutron Bombardment.*—The three methods of neutron bombardment mentioned above differ by several orders of magnitude in their efficiency.

A radium–beryllium source, containing 1 g. of radium carefully mixed in the form of its chloride with 5 g. of the finest beryllium powder, emits per second about 10^7 neutrons.[5] A cyclotron of the size of the Berkeley machine (diameter of the magnet about 60″), running with an output of 50 μA, can produce 4×10^{12} neutrons per second. A uranium pile, operated at 1000 kw., yields as much as 6×10^{16} neutrons per second.

The differences in efficiency are, however, not quite so great as suggested by the above figures. Owing to the smallness of a radium–beryllium source it will usually be possible to utilise its total neutron radiation ; and most of the neutron flux of a cyclotron is also, at least theoretically, available for experiments. In the pile, however, almost all the neutrons produced by the fission of ^{235}U atoms are used up in either splitting other ^{235}U atoms or in being captured by ^{238}U atoms ; the pile can only be operated safely if these two processes account for most of the neutrons liberated, and no more than some 10^{15} neutrons per second are available for tracer production. Even so, the efficiency of the pile is about a thousand times that of a big cyclotron, and a hundred million times that of a fairly " strong " radium–beryllium source.

It would seem, therefore, that, as far as quantity of output is concerned, the uranium pile could take over the world production of tracers. There is in fact, no doubt that during the next few years the tracers to be used in laboratories all over the world will mainly come from the uranium piles of the United States and, to a lesser extent, from those of Britain and Canada. But it would be erroneous to suppose that the other methods of production will be insignificant. First of all, most of the radio-nuclides formed in the pile must belong to the group which have more neutrons than their stable isotopes ; they may be produced by an (n,γ), or an (n,p), or an (n,α) reaction, examples of which are :

$$^{31}_{15}\mathrm{P} + {}^{1}_{0}n \longrightarrow {}^{32}_{15}\mathrm{P} + \gamma \qquad {}^{6}_{3}\mathrm{Li} + {}^{1}_{0}n \longrightarrow {}^{3}_{1}\mathrm{H} + {}^{4}_{2}\mathrm{He}$$

$$^{31}_{15}\mathrm{P} + {}^{1}_{0}n \longrightarrow {}^{31}_{14}\mathrm{Si} + {}^{1}_{1}\mathrm{H}$$

The first two reactions obviously lead to nuclides in which the proportion of neutrons to protons is increased and which are, therefore, heavier than their stable isotopes. If we consider that the same is true of the fission products, we realise that, for the production of the second group of nuclides, *viz.*, those which are too light to be stable, another mode of production is necessary. For this group, the cyclotron or another of the machines with resonance acceleration can be used. The newly discovered " splintering reactions ", in which under the impact of particles of several hundred electron

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[5] H. L. Anderson and B. T. Feld, *Rev. Sci. Instr.*, 1947, **18**, 186.

volts a nucleus loses a considerable number of its protons and neutrons,[6] are particularly effective in creating such neutron-deficient, and therefore positron-emitting, nuclides.

But also in some cases where both methods are applicable, the cyclotron may have the advantage of yielding radio-nuclides of higher specific activity. There are limits to what can be obtained in this respect in the pile, because here in the central region, where the densest neutron flux obtains, a high proportion of the neutrons are not yet slowed down and, therefore, unsuitable for some reactions ; further away from the centre, the neutron density is smaller. In the cyclotron, concentration of the beam on a small target is frequently able to produce the desired specific activity where chemical concentration is impossible, as in the case of (d,p) reactions (see p. 99).

Furthermore, short-lived tracers cannot be transported far from their place of origin ; those produced in a pile will have to be used on the spot, and countries not possessing a uranium pile will continue to prepare these tracers by the use of cyclotrons or high-tension sets.

For many laboratories also the radium–beryllium source will retain its value as an extremely simple and constant producer of neutrons ; instead of radium, radon can be used. The neutrons are generated according to the processes

$$^{9}_{4}\mathrm{Be} + {}^{4}_{2}\mathrm{He} \longrightarrow {}^{12}_{6}\mathrm{C} + {}^{1}_{0}n \quad \text{or} \quad 3\,{}^{4}_{2}\mathrm{He} + {}^{1}_{0}n$$

The preparation of an efficient radon–beryllium source has been recently described in detail.[5]

(B) *Deuteron Bombardment.*—Deuteron bombardment can only be effected by a cyclotron or another instrument which accelerates charged particles. Its application in tracer production is twofold. The deuterons may either be made to hit directly the element from which the tracer is to be obtained, or they may be used to create neutrons which then, in their turn, produce the tracer nuclide. The usual targets for the second application are beryllium and lithium, according to the reactions :

$$^{9}_{4}\mathrm{Be} + {}^{2}_{1}\mathrm{H} \longrightarrow {}^{10}_{5}\mathrm{B} + {}^{1}_{0}n$$
$$^{7}_{3}\mathrm{Li} + {}^{2}_{1}\mathrm{H} \longrightarrow {}^{8}_{4}\mathrm{Be} + {}^{1}_{0}n \quad \text{or} \quad 2\,{}^{4}_{2}\mathrm{He} + {}^{1}_{0}n$$

Beryllium targets can better withstand the high deuteron beam currents than lithium targets, but the lithium reaction gives neutrons of higher energy. The number of neutrons produced is no more than a fraction of the primary deuterons and even at high energies does not exceed 0·2%. This explains the relative inefficiency of the cyclotron as neutron source (see p. 96).

For the direct production of tracer nuclides the target to be hit by the deuteron beam can be placed either inside the cyclotron vacuum chamber, or outside. In the first case we make better use of the whole deuteron beam, but the temperature created in the vacuum will be too high for many materials, even if we try to cool the target from one side by water, or use other cooling devices ; if on the other hand, the sensitive target material is

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[6] G. T. Seaborg, *Chem. Eng. News*, 1947, **25**, 2819.

placed outside the cyclotron in a special chamber which the deuteron beam enters through a metal-foil window, we may cool the target much more efficiently by surrounding it by helium gas. For inside bombardment we have frequently to use chemical compounds instead of the elements, for instance, a phosphide instead of elementary phosphorus, thus reducing in the target area the number of the phosphorus atoms, but gaining not only higher heat resistance but also the advantage of a better-conducting contact with the water-cooled target support.

Several of the deuteron reactions in the cyclotron permit the production of nuclides which are not obtainable in the pile (cf. p. 96), *e.g.*, ^{22}Na and ^{55}Fe, with half-lives of 3 and 4 years, respectively; other isotopes of the same elements, ^{24}Na and ^{59}Fe, with half-lives of 14·8 h. and 44 d., are better produced in the pile. The reactions are:

$$^{24}_{12}\text{Mg} + ^{2}_{1}\text{H} \rightarrow ^{22}_{11}\text{Na} + ^{4}_{2}\text{He} \qquad ^{23}_{11}\text{Na} + ^{1}_{0}n \rightarrow ^{24}_{11}\text{Na} + \gamma$$

$$^{55}_{25}\text{Mn} + ^{2}_{1}\text{H} \rightarrow ^{55}_{26}\text{Fe} + 2^{1}_{0}n \qquad ^{59}_{27}\text{Co} + ^{1}_{0}n \rightarrow ^{59}_{26}\text{Fe} + ^{1}_{1}\text{H}$$

(C) *Uranium Fission.*—The fission products of ^{235}U comprise radioactive isotopes of the elements $_{30}$Zn to $_{63}$Eu. Many of them are valuable as tracers thanks to the convenient properties of their radiations and half-lives. Some, however, are followed by a long chain of disintegration products which limit their usefulness (see p. 95). The total activity of all the fission products in a pile is tremendous; from a 1000 kw. pile more than 1 million curie are available. So the problem is here mainly one of safeguarding the workers against medical danger if—after most of the activity has decayed—the separation of pure tracer material is attempted.

Since the extraction of the fission products can only be carried out when the uranium metal is dissolved for the manufacture of plutonium, this method of tracer production is less suitable for their routine supply than the neutron absorption by non-fissionable substances which are exposed for a limited period to the neutron flux in the pile. None of the fission products of the U.S.A. piles is at present offered for export (cf. p. 105).

It ought to be mentioned that fission products can also be obtained by the neutron bombardment of uranium in a cyclotron, but the yield is, of course, much smaller.

(III) *Analytical Separation and Concentration of the Nuclides*

After the desired nuclide has been produced by one of the methods outlined in the preceding section, it will be the task of the chemist to free it as far as possible from the accompanying substances and thus prepare it in the highest specific activity obtainable. The chemical procedure, and the results, will be quite different according to whether or not the tracer nuclide is isotopic with the stable atomic species from which it has been produced.

Most of the slow neutron reactions consist in the capture of the neutron in the nucleus without the emission of a charged particle; consequently, the new radioactive atom is isotopic with its parent, and no chemist is able, by the usual laboratory processes, to separate the two once complete mixing has taken place. The maximum specific activity in these cases is determined by the percentage of atoms converted during the bombardment; and all the chemist can do is to separate the two isotopes together from the other elements. Formally equivalent to these (n,γ) reactions are the (d,p) reactions in the cyclotron.

If we speak of the chemical inseparability of isotopes, it is always understood that they have been completely mixed; if, however, from the start they have been in a different physical or chemical state, then their reactions may be different and allow of a partial or complete separation. L. Szilard and T. A. Chalmers [7] have pointed out that in most cases the neutron capture by an atom will not only cause a change in its nuclear structure, but also the breaking of its chemical linkage; the resulting new atoms, although isotopes of the same element, will therefore no longer be present as part of the same molecules; a separation, and consequently an increase of the specific activity, should, therefore, be possible. This consideration will, however, not be valid, if the chemical linkage in which the old atoms are held is of the kind which permits of a quick interchange with the new isotopes; therefore, if we intend to make use of the Szilard–Chalmers effect for obtaining a high specific activity of an isotopic tracer, we have to choose the target material carefully so as to avoid the possibility of such exchange processes. Unfortunately, the chemist will not always be able to give good advice here; more study will be necessary before full use can be made of the possibilities opened up by Szilard and Chalmers.

The situation is quite different in all the other cases where the tracer substance produced is not isotopic with its parent. The task of the chemist is then the separation of two different chemical elements, and ordinary analytical chemistry should provide the necessary knowledge. As a matter of fact, the well-known analytical processes actually form the basis of all the operations of tracer purification, but in two respects the chemist's handling of a radioactive substance is likely to encounter special difficulties.

First of all, the radiation emitted by the material may introduce complications. We are not concerned here with the important question of protection against health hazards. To devise laboratories with appropriate shielding by lead or concrete, and with machinery for the performance of the chemical operations by remote control, is largely a problem for the builder and engineer; the chemist will only be compelled to select the simplest possible processes in order not to make the engineer's task too difficult. But even when the operator is safeguarded, the radiations will still be efficacious inside the solutions or gases the chemist has to deal with, causing here a variety of chemical changes. For instance, in any aqueous solution hydrogen and hydroxyl radicals will be produced, and these radicals will then act in different ways upon the solute.[8] A knowledge of " radiation chemistry " (*i.e.*, chemical changes under the influence of radiations) is, therefore, important in " radiochemistry " (*i.e.*, the chemistry of the radioactive elements).

[7] *Nature*, 1934, **134**, 462.

[8] J. Weiss, *ibid.*, 1944, **153**, 748.

While this first disturbance becomes the more disagreeable the greater the amount of radioactive material and, consequently, the strength of its radiation, quite the opposite is true of the second complication; here the difficulties are, generally speaking, the more marked the smaller the number of atoms the radio-chemist has to deal with. Compared with ordinary chemistry, the quantity of matter he has to handle is almost invariably insignificant, but it is expedient to distinguish three different ranges of weight to which it may belong, the limits being roughly the following:

(1) Microchemical quantities, from 10^{-2} g. to 10^{-4} g.
(2) Ultramicrochemical quantities, from 10^{-4} g. to 10^{-7} g.
(3) Invisible quantities, less than 10^{-7} g.

In the first range, the methods are still those of ordinary chemistry, with a somewhat refined technique. For the analysis of organic substances, these improvements are well known thanks to the work of F. Pregl; he introduced to wider circles the micro-balance which can measure with an accuracy of 10^{-6} g. On similar lines, but on a broader basis, the inorganic microchemistry of this region was worked out in Graz by F. Emich [9] and his school.

Operations in the ultramicrochemical region were attempted somewhat later by chemists of the same school, especially A. A. Benedetti-Pichler (now in New York) and his pupil M. Cefola,[10] and during the last war were taken up by radio-chemists (P. L. Kirk, and others in G. T. Seaborg's group).[11] They took their lead partly from biologists who had previously developed the technique of working under the microscope with the help of a micromanipulator. For weight determinations quartz-fibre balances of different patterns are used; the accuracy of some of them reaches 2×10^{-8} g.

Even in the ultramicrochemical region the chemical processes are the familiar ones; by reducing the size of the vessel and the quantity of the liquid to, say, 10^{-5} c.c., it is for instance possible directly to determine in the usual way the solubility of a salt of which only a few micrograms are available. This technique proved most valuable in the exploration of the chemistry of the new radio-element plutonium after it had been produced in barely visible quantities. But the real peculiarities of radiochemistry are only revealed if we go down to invisible and unweighable quantities of matter; their behaviour depends, naturally, largely on that of the other substances present, but contrary to the expectations of many, even quantities of matter of 10^{-12} g. or less per litre have a definite chemistry of their own, as emphasised by F. Soddy already in the early days of radiochemistry.

In dealing with invisibly small amounts of a radio-element the chemical operations can usually be much simplified by the addition of a trace of an inactive isotope; by this artifice we can without any difficulty raise the

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[9] See F. Emich, " Lehrbuch der Mikrochemie ", J. F. Bergmann (Munich, 1926).

[10] See A. A. Benedetti-Pichler, " Introduction to the Microtechnique of Inorganic Analysis ", Chapman & Hall (New York, 1942).

[11] See G. T. Seaborg, *Chem. Eng. News*, 1946, **24**, 1192.

total concentration of the element (consisting now of two isotopes) into the microchemical or even macrochemical region. But it must be remembered that such a procedure reduces the specific activity of the radioactive substance irreversibly, since isotopes are inseparable by ordinary methods. The problem of concentrating the radio-elements without the addition of an isotope is therefore the fundamental problem of radiochemistry.

No generally valid way to solve this problem can be told to the analytical chemist. It can, however, be stated that invisible amounts of a metal are generally carried down with any precipitate whose anion forms an insoluble compound with this metal.[12] If, *e.g.*, traces of bismuth are to be removed from a solution, it suffices to precipitate therein lead sulphide ; the anions of the lead sulphide precipitate then carry down the bismuth, because bismuth sulphide is insoluble ; a precipitate of lead sulphate on the other hand would not act in the same way as a " carrier " because bismuth sulphate is soluble. This precipitation rule was established as early as 1914 ; since then many attempts have been made to replace it by a stricter " precipitation law ",[2] but with little success.

The advantage of a non-isotopic carrier is that we retain the possibility of a further concentration of the radio-element in later stages of the analytical process ; this operation may be effected by attaching the radio-element to smaller quantities of another carrier, or by completely changing the procedure. Very often electro-chemical deposition is the most satisfactory final method for obtaining a radio-element with the minimum amount of foreign matter. The same result may sometimes be achieved by solvent extraction, or by distillation. The choice of the method will frequently be influenced by the time factor ; it is obvious that for rapidly-decaying tracer substances only quick-working processes are suitable.

As the efficient chemical extraction of the radioactive nuclide is an essential condition for the success of the whole tracer experiment, the voice of the chemist ought to be heard already in the discussion on the best process for its production. For instance, the important tracer ^{11}C has a half-life of only 20 mins. ; it can be produced by deuteron bombardment of boron atoms : $^{10}_{5}\mathrm{B} + ^{2}_{1}\mathrm{H} \rightarrow ^{11}_{6}\mathrm{C} + ^{1}_{0}n$. Now from a physicist's point of view, elementary boron would seem to be the best target because it possesses the densest packing of boron atoms ; but the ^{11}C atoms produced therein cannot be recovered without the time-consuming process of oxidation at high temperature. If, however, boron oxide, B_2O_3, is used as a target, the ^{11}C atoms, expelled by recoil and present in the highly reactive state of free, or " hot " atoms, have a good chance of combining with one of the oxygen atoms ; and as the B_2O_3 target melts under the heat of the deuteron beam, the majority of the ^{11}C atoms escape during the bombardment as gaseous ^{11}CO, which can be easily collected.[13]

Usually a compromise will have to be reached between the physicist's

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[12] F. A. Paneth, *Physikal. Z.*, 1914, **15**, 924 ; *Jahrbuch der Radioaktivität und Elektronik*, 1915, **11**, 451 ; K. Horovitz und F. A. Paneth, *Z. physikal. Chem.*, 1915, **89**, 513 ; K. Fajans and F. Richter, *Ber.*, 1915, **48**, 700.

[13] S. Ruben, M. D. Kamen, and W. Z. Hassid, *J. Amer. Chem. Soc.*, 1940, **62**, 3443.

and the chemist's point of view. One of the tracers most used in biological work is ^{32}P ; if no uranium pile is available, the following deuteron reaction of the cyclotron is one of the most convenient ways : $^{31}_{15}P + ^{2}_{1}H \rightarrow ^{32}_{15}P + ^{1}_{1}H$. For reasons given above, elementary phosphorus which would be ideal for the subsequent chemical treatment, cannot be used as internal target ; in its stead ferrous phosphide, soldered to a water-cooled copper target, is bombarded by the deuterons, with the consequence that the chemist later has the task of separating the phosphorus from the iron, and purifying it from traces of copper and various radio-elements resulting from the deuteron bombardment of the iron. Instead of the rather laborious process described in the literature,[14] K. F. Chackett and F. Morgan, in the Londonderry Laboratory for Radiochemistry in Durham, have found the following procedure very satisfactory as regards speed as well as efficiency. If the target is heated in a stream of chlorine gas, the phosphorus, as PCl_5, and the iron, as $FeCl_3$, are distilled off ; after removal of the chlorine and reduction, by hydrogen, of the $FeCl_3$ to $FeCl_2$, the phosphorus alone, as PCl_3, is volatile and can be collected in water and then converted into phosphoric acid or sodium phosphate, whichever is desired.

One point which the chemist is anxious to stress is the necessity of using in the targets material of the highest chemical purity. Mere traces of unexpected impurities may cause considerable trouble, especially if the chemist has to attain a prescribed specific activity and is not permitted to overcome difficulties by the addition of an isotopic carrier (see above). Purification of the target material is always much easier before the irradiation than afterwards when minute amounts of radioactive substances contained therein have to be preserved, and the time allowed for the work may be limited by the short half-life of some of them.

(IV) *Synthesis of the Tracer Substance*

After the radioactive nuclide in the desired specific activity has been produced by the physicist and extracted by the analytical chemist, it has to be incorporated in the proper tracer substance. If only the path, or the distribution, of the whole tracer molecule has to be studied, it will suffice to know that the radioactive atom is contained therein ; but very frequently, especially in the field of biochemistry, changes in the molecule itself are the object of study, and then the introduction of the active atom into a well-defined position of the molecule becomes imperative. For this reason the synthesis—often on a very small scale—of compounds of biological importance containing the active nuclide has become an integral part of tracer technique.

One of the major difficulties encountered here is the necessity of performing all the chemical operations within a period not much in excess of the life-time of the radioactive atom ; only if at the beginning activities of a much higher order than needed for the experiment are available, is it possible to spend, say, ten life-times of the radio-element on chemical

[14] R. R. Wilson and M. D. Kamen, *Physical Rev.*, 1938, **54**, 1031.

manipulations, thus reducing its activity to less than 1 per mille. It is clear that a saving of time will frequently much more than compensate for a loss of material in the synthesis, and the chemist will have to devise his method accordingly.

In some fortunate cases the synthesis of the described tracer substance, or at least of an intermediate compound, takes place automatically during the production of the radio-nuclide. We have mentioned above the formation of the useful ^{11}CO from bombarded boron oxide. The ^{11}C atoms, after their formation out of boron, react preferably with the abundant oxygen atoms, though some of them apparently combine with the boron and form boron carbide; this explains the difficulty of removing a fraction of the ^{11}C atoms from the target. Such reactions of " hot " atoms also play an important rôle in liquid systems and are likely to obscure the scope of the Szilard–Chalmers effect. According to their ideas, it was to be expected that if, *e.g.*, ethyl or methyl bromide is irradiated with neutrons, every bromine atom capturing a neutron and consequently emitting a γ-ray, would acquire sufficient recoil energy to become detached from the alkyl group. Such bromine atoms can be extracted by simply shaking the ethyl bromide with water; but the yield found was rather disappointing and it appeared as though many bromine atoms, although activated, were still " retained " by their original molecules. A closer study has shown,[15] however, that beside the alkyl bromide there were now new bromine compounds present in the organic phase, and it is very likely also that the methyl and ethyl bromide molecules containing active bromine were not the original molecules, but had their inactive bromine dislodged by a radioactive and chemically hot bromine from another molecule. This interpretation receives strong support from the fact that in gaseous ethyl bromide more than 97% of the activated bromine atoms could be proved to be separated from the ethyl groups.[16]

We mention these observations here because some of the " new " bromine molecules which are formed as an immediate consequence of the bromine activation may be valuable as tracer substances; likewise, we may directly obtain several different organic iodine compounds suitable for tracer experiments by treating alkyl iodides with neutrons.

Somewhat similar observations were made on the chemical combinations into which hot ^{14}C atoms enter. This very important tracer material is produced from nitrogen by neutron bombardment: $^{14}_{7}N + ^{1}_{0}n \rightarrow ^{14}_{6}C + ^{1}_{1}H$.

Usually, as nitrogen-containing target, saturated solutions of ammonium nitrate in water are chosen; if so, most of the ^{14}C appears as carbon mon- or di-oxide; but methane, methanol, formic acid, and other simple molecules containing ^{14}C were also found.[17] If beryllium nitride is used as a target, the hot ^{14}C atoms apparently combine partly with the beryllium, and the radio-carbide $Be_2{}^{14}C$, on treatment with water, gives active methane.[18]

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[15] E. Gluckauf and J. W. J. Fay, *J.*, 1936, 390.

[16] H. Suess, *Z. physikal. Chem.*, 1940, *B*, **45**, 297.

[17] P. E. Yankwich, G. K. Rollefson, and T. H. Norris, *J. Chem. Physics*, 1946, **14**, 131.

[18] P. E. Yankwich, *ibid.*, 1947, **15**, 374.

Interesting though these automatic syntheses are, they do not lead very far, and for all the more complicated organic molecules the skill of the chemist is necessary. Since both ^{11}C and ^{14}C are most easily obtained as carbon monoxide or dioxide, as a first step the conversion of these gases into a compound more useful for organic syntheses is desirable. An elegant method has recently been devised [19] which permits work on as little as 50 microlitres of carbon dioxide and affords within a few minutes almost complete conversion into acetylene.

A more complicated way for the change of carbon dioxide into acetylene had to be used previously in connection with the successful attempt to introduce ^{11}C into different positions in the lactic acid molecule, labelling either the carbon atoms in the carboxyl group, or those in the α- and β-positions. The methods employed [20] can be seen from the schemes :

$$\text{(i) } \overset{*}{C}O_2 \xrightarrow{K,\ NH_3} K\overset{*}{C}N \xrightarrow{CH_3\cdot CHO} CH_3\cdot CH(OH)\cdot\overset{*}{C}N \xrightarrow{\text{hydrolysis}} CH_3\cdot CH(OH)\cdot\overset{*}{C}O_2H$$

$$\text{(ii) } \overset{*}{C}O_2 \xrightarrow{NaOH\ ;\ BaCl_2} Ba\overset{*}{C}O_3 \xrightarrow{Mg} Ba\overset{*}{C}_2 \xrightarrow{H_2O} \overset{*}{C}_2H_2 \xrightarrow{HgSO_4\ ;\ H_2SO_4} \overset{*}{C}H_3\cdot\overset{*}{C}HO \xrightarrow{KCN}$$

$$\overset{*}{C}H_3\cdot\overset{*}{C}H(OH)\cdot CN \xrightarrow{\text{hydrolysis}} \overset{*}{C}H_3\cdot\overset{*}{C}H(OH)\cdot CO_2H$$

Even more complicated organic syntheses have been performed with radioactive nuclides ; attention may be directed to a paper [21] in which the fate of methionine in the animal body was studied with the help of molecules of this substance containing active sulphur in addition to two active carbon atoms in the following positions :

$$CH_3\cdot\overset{*}{S}\cdot\overset{*}{C}H_2\cdot\overset{*}{C}H_2\cdot CH(NH_2)\cdot CO_2H$$

In some cases biological action can be utilised in the preparation of complicated tracers. R. D. Evans and his collaborators,[22] in their studies on red blood corpuscles, started by labelling the iron in ferric ammonium citrate by mixing it with both ^{55}Fe and ^{59}Fe ; a solution of this active citrate was injected intravenously into humans ; both tracer substances entered by exchange processes into the iron content of the blood ; so, later, the radioactive red blood cells of these " donors " could be transfused and traced in the bloodstream of other humans. The combined use of two tracers of half-lives of 4 years and 44 days made this tracer method particularly flexible and valuable.

Such " biosyntheses " can be performed also by micro-organisms. The so-called methanobacterium reduces carbon dioxide to methane in the fermentation of ethyl alcohol to acetic acid :

$$2C_2H_5\cdot OH + \overset{*}{C}O_2 \longrightarrow 2CH_3\cdot CO_2H + \overset{*}{C}H_4.$$

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[19] W. J. Arrol and R. Glascock, *Nature*, 1947, **159**, 810.

[20] R. D. Cramer and G. B. Kistiakowsky, *J. Biol. Chem.*, 1941, **137**, 549 ; B. Vennesland, A. K. Solomon, J. M. Buchanan, R. D. Cramer, and A. B. Hastings, *ibid.*, 1942, **142**, 371.

[21] G. W. Almer and V. du Vigneaud, *ibid.*, 1944, **154**, 247.

[22] *J. Clin. Invest.*, 1946, **25**, 605.

In an hour or so a few millimoles of labelled methane can thus be formed.[23] Other bacteria, in the presence of active carbon dioxide, produce labelled lactic, acetic, and succinic acids, and as there is a great variety of micro-organisms available, the method seems well worth further study.

Availability of Tracers

As this Review had to deal only with the preparation of radioactive tracers, no mention has been made of any problem which we may hope to solve by their application ; however, in most cases the real scientific interest of the work starts after the preparation of the tracer, when we begin to use it. For this reason most scientists will be the happier the less they have to worry about the manufacture of the tracers they need, and it is very desirable that central organisations should be built up to carry out the preparation of tracers for the benefit of all the laboratories that want them. In this way also the costs for the tracers can be very substantially reduced. As an example, it may be mentioned that the price for 1 mc. of ${}^{14}_{6}C$ which is of such inestimable value for biochemical research, if produced by a cyclotron, amounts to about $1,000,000 ; as a product of the Clinton uranium pile it is sold in the U.S.A. for $50.

Until recently other countries could not benefit from this development, because the wealth of radioactive tracers produced in the U.S.A. uranium piles, and distributed in that country, was excluded from export, and even the scientific experience gained by those who had been engaged in making and separating the various tracer substances was not completely available to other scientists. The restrictions, however, on the distribution of scientific information are diminishing, and it was most welcome news when last September President Truman, in a telegram to the International Cancer Congress, announced that most of the tracer substances available to U.S.A. scientists may now also be sent abroad. In Table I (p. 94) the tracers whose export has thus been allowed, are marked by an asterisk.[24]

In Great Britain the purchase of tracers from the U.S.A. will probably not be necessary for long. It is expected that in about a year the high-energy pile at present under construction at the Atomic Energy Research Establishment at Harwell (Berkshire) will be in operation. The graphite low-energy experimental pile (" GLEEP ") which is already running there is not able to produce more than small amounts of a few urgently needed tracers ; the manufacture of a greater variety of tracers, and in larger quantities, can begin only when the bigger pile is working ; but then the position in this country should be very similar to that in America, *i.e.*, practically all the tracer material needed by scientific laboratories will be obtainable from the Government. It is intended to send the irradiated material first to a Radiochemical Centre instituted by the Government at

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[23] H. A. Barker, S. Ruben, and M. D. Kamen, *Proc. Nat. Acad. Sci.*, 1940, **26**, 426.

[24] Details of the procedure for requesting and purchasing these tracers can be found in the Catalogue and Price List on " Radio-isotopes for International Distribution ", issued Sept. 1947 by the Isotope Branch of the U.S. Atomic Energy Commission (P.O. Box E., Oak Ridge, Tennessee).

Amersham (Buckinghamshire) where the separation and concentration of the tracers will be done ; in the case of tracers, however, which have been produced by an (n,γ) reaction and can therefore not be separated from their isotopes, the aluminium containers in which the irradiation will be effected may also be sent directly from the pile to the research laboratories. Although American tracer material is at the present moment not available to industrial laboratories in England, no such restriction is intended for the material produced at Harwell.

Finally, it should be mentioned that a third place is also ready to start tracer production, the uranium–heavy water plant in Chalk River (Ontario) in Canada ; it is certain that from there, too, tracer material will be obtainable in the near future, but details have not yet been announced.