LETTERS TO THE EDITORS

Re: Terminology Concerning Specific Activity of Radiopharmaceuticals

In the manufacture of artificial radionuclides, the assumption is frequently made that if no stable isotopes of the element being produced are knowingly introduced, the resultant radionuclide is "carrier-free," i.e., it contains only the nuclide of interest. However, there is increasing use of short-lived isotopes of elements widely distributed in our environment, radionuclides that have theoretical specific activities in the mCi/pmole range, and the probability of accidental dilution with stable isotope has to be considered. Modern nonradioactive analytical techniques have developed to the stage where picomole quantities of material are routinely detected (and sometimes femtomole quantities), and radioactive tracers are being applied to systems that will saturate at or below nanomole quantities of material.

Thus at present there are tracer studies that require specific activities approaching the theoretical limits, and analytical methods are available to measure the actual amounts of material present at the required levels. However, in many cases in the literature the term "carrier-free" is used when there has been no determination of actual specific activities, and the chances of significant dilution with stable isotopes approach certainties.

There is a growing awareness of this problem (*1-6*) and a recent article suggested that the term "carrier-free" be reserved for those cases in which it can be justified (*1*).

A brief survey of recent articles (*2,4,6*) suggests that there is confusion even among chemists as to the use of the term "carrier-free," and we would like to suggest that the leading journals establish a policy of limiting its use along the lines previously suggested (*1*). This then raises the question of what to term the majority of current so-called "carrier-free" procedures in which the specific activity, although undoubtedly high, has not been measured. The term "no carrier added" has the virtue of being clear and self-explanatory (*1*), although it is not easy on the tongue.

Adoption of this policy would serve to emphasize the problems of high-specific-activity synthesis for those directly involved in the chemistry and to clarify the situation for those who use the tracers.

T. J. TEWSON
University of Texas
Houston, Texas

M. J. WELCH
Washington University School of Medicine
St. Louis, Missouri

ACKNOWLEDGMENT

Research carried out at Brookhaven National Laboratory is under contract with the U.S. Dept. of Energy and is supported by its Office of Basic Energy Sciences.

REFERENCES

1. WOLF AP, FOWLER JS: Organic radiopharmaceuticals, recent advances. In *Radiopharmaceuticals II. Proceedings of the 2nd International Symposium on Radiopharmaceuticals, Seattle, Washington.* New York, The Society of Nuclear Medicine, 1979, pp 72-93
2. BERGER G, MAZIERE N, SASTRE J, et al: Carrier free ^{11}C formaldehyde. An approach. *J Lab Cmpds and Radiopharm* 17:59-71, 1979
3. NOZAKI T, IWAMOTO M, ITOH Y: Production of ^{77}Br by various nuclear reactions. *J Appl Radiat Isot* 30:79-83, 1979
4. COENEN HH, MACHULLA H-J, STOCKLIN G: Practically carrier-free labelling of aromatic compounds with bromine-77. *J Lab Cmpds and Radiopharm* 16:897-907, 1979
5. IWATA R, IDO T, SAJI H, et al: A remote controlled synthesis of ^{11}C-iodomethane for the practical preparation of ^{11}C-labelled radiopharmaceuticals. *J Appl Radiat Isot* 30:194-196, 1979
6. TEWSON TJ, WELCH MJ: Preparation and preliminary biodistribution of "no carrier added" fluorine-18 fluoroethanol. *J Nucl Med* 21: 559-564, 1980

Reply

The term "carrier" had its origins in the early work of Kasimir Fajans, Fritz Paneth, and Otto Hahn. It was applied to cocrystallization and coprecipitation phenomena observed during research with naturally occurring radionuclides. In a now classic text titled *Radioactivity Applied to Chemistry* (*1*) Bonner and Kahn had written a chapter on "Behavior of Carrier-Free Tracers" in which "Carrier-free" was communicated as follows: "However, it is [customary] to refer to all radioactive preparations to which no isotopic carrier has been intentionally added and containing no isotopic material detectable by [ordinary] chemical or spectrographic means as *carrier-free*." This definition was applied to a wide variety of coprecipitation studies and only incidentally to the question of carrier where the "isotope" and its carrier are made of nuclides of the same element or nuclides of the same element in the same chemical compound assuming accepted purity criteria. The term "carrier-free" and related terms have clearly been widely misused in the rigorous sense, and we too have been guilty of imprecise use of these terms.

Recent advances in nuclear medicine and in radiopharmaceuticals have prompted us to reassess the common usage. Advances in analytical techniques, including wholly new approaches to chemical analysis, have greatly extended the range of accurate detection of chemical species. Nuclear medicine research and application is becoming increasingly concerned with the use of organic and organometallic compounds that must be used at the true tracer level. An example is the use of labeled compounds to probe receptor sites in the brain or heart where the number of sites available and/or occupied is germane to the particular study. The increasing sophistication of physiological and biochemical models requires a knowledge of changing specific activity during the course of the study or procedure when the initial material is not truly "carrier-free."

It is for these reasons and others that the adoption of more rigorous definitions of terms was suggested at the Second International Symposium on Radiopharmaceuticals held in Seattle in 1979 by the Society of Nuclear Medicine and reiterated at the Third International Symposium on Radiopharmaceutical Chemistry held in St. Louis in 1980.

Three unambiguous terms can be defined:

1. "Carrier-free" (CF) should mean that the radionuclide or stable nuclide is not contaminated with any other stable or radioactive nuclide of the same element.

2. "No carrier added" (NCA) should apply to an element or compound to which no carrier of the same element has been intentionally or otherwise added during its preparation.

3. "Carrier added" (CA) should apply to any element or compound to which a known amount of carrier has been added.

It should be clear that these terms refer to a specific position or positions when applied to a molecule.

The term "carrier-free" (CF) is the most difficult to quantitate. It should only be used when evidence is provided that the element or compound is indeed carrier free. There are very few examples at present where this might even be possible. It may be useful to modify this term slightly by using "near carrier-free" (NCF), followed by an obligatory quantitation, such as ^{18}F-NCF (1% of all fluorine atoms in the compound at assay time are stable fluorine).

The term "no carrier added" (NCA) applies to the vast majority of elements and compounds to which the term "carrier-free" is incorrectly applied. The problems in technetium chemistry are well known. Whereas many of the preparations of ^{11}C-carbon monoxide are of "high" specific activity, none in the literature today are demonstrably CF, indeed they are far from it! If known, the term "NCA" can also be qualified with a statement of precise or approximate dilution.

The term "carrier-added" (CA) is obvious and again should be qualified with precise data if available

The use of these three simple terms CF, NCA, and CA would immediately identify for the reader the extent of dilution of the tracer and simplify the evaluation of utility in those cases where precise nuclidic, radioactive, or other composition is *necessary* information for the study. If nothing else, their use would remove a source of confusion and misdirection in the scientific literature.

ALFRED P. WOLF
Brookhaven National Laboratory
Associated Universities, Inc.
Upton, New York

REFERENCE

1. WAHL AC, BONNER NA, Eds: Behavior of carrier-free tracers. In *Radioactivity Applied to Chemistry*. New York, John Wiley and Sons, 1951

Re: Simultaneous Treatment of Toxic Diffuse Goiter with I-131 and Antithyroid Drugs: A Prospective Study

Recently in the *Journal* Steinbach, Donoghue, and Goldman reported a decreased incidence of hypothyroidism after I-131 therapy for diffuse toxic goiter in patients who were receiving antithyroid drugs compared with those who were not (*1*). They reported that the estimated thyroid weights for determination of the I-131 doses were obtained from thyroid scans "using the Bauer-Blahd formula," but did not report the actual estimated weights. Application of their tabulated data and their dosimetry formula appears to show an average estimated thyroid weight of 91 g for patients who received I-131 alone and 77 g for patients who received both I-131 and antithyroid drugs.

In another recent *Journal* article, Tamagna, Levine, and Hershman reported a considerably lower average estimated thyroid weight of 43 g in 12 patients with diffuse toxic goiter "based on planimetry of the thyroid scan" (*2*). Their series also consisted of mostly male patients, although their patients were presumably from California rather than from New York.

The discrepancy between the average estimated thyroid weights in the two studies suggests the possibility that Steinbach, Donoghue, and Goldman may consistently derive higher estimates of thyroid weight than at least some other physicians might. If so, perhaps they could decrease the incidence of hypothyroidism after I-131 therapy in their patients by merely revising their technique for estimating thyroid weight rather than by adding antithyroid drugs to their regimen.

FREDERICK N. HEGGE
Emanuel Hospital
Portland, Oregon

REFERENCES

1. STEINBACH JJ, DONOGHUE GD, GOLDMAN JK: Simultaneous treatment of toxic diffuse goiter with I-131 and antithyroid drugs: A prospective study. *J Nucl Med* 20:1263-1267, 1979
2. TAMAGNA EI, LEVINE GA, HERSHMAN JM: Thyroid-hormone concentrations after radioiodine therapy for hyperthyroidism. *J Nucl Med* 20:387-391, 1979

Reply

Dr. Hegge comments on an apparent discrepancy in the thyroid gland weight between our study (*1*) and that performed by Tamagna et al. (*2*). He then concludes that by revising the calculation of the thyroid weight alone the incidence of hypothyroidism could be reduced.

Dr. Hegge has quite reasonably arrived at the mean thyroid weights in our series. Our data show this mean weight to be 85 g (range 24-190 g) for Group A and 72 g (range 33-239 g) for Group B.

Our data quite obviously differ from those of Tamagna et al. (*2*), and any of the following could account for the differences: (a) patient selection—random (*1*) contrasted with selective (*2*); (b) type of patients—all male (*1*) contrasted with 21% female (*2*); (c) geographical location—Great Lakes (*1*) contrasted with West coast (*2*); (d) type of goiter—toxic diffuse only (*1*) contrasted with toxic diffuse and nodular (*2*). In addition, the number of patients in either study is too small to be representative of any particular population.

In another study by Blahd and Hays (*3*) done on 241 male hyperthyroid patients at the Wadsworth VA Hospital in California, the mean thyroid gland weight was 51 ± 28 g.

Dr. Hegge's suggestion that reduction in thyroid weight used for calculation—i.e., reduction of the dose administered to the thyroid—will result in decreased incidence of hypothyroidism is not a novel one. A vast amount of literature is available on this subject (some of it referred to in our original paper). Dr. Hegge, however, has ignored the difference in results for the two groups we reported. Group A had a very low incidence of hypothyroidism (8%) and Group B had an incidence (36%), which is no different from other reported series (*4*,*5*). Since gland weight was calculated in the same manner for both groups, it could not account for the difference in outcome.

Finally, Dr. Hegge has suggested revision of our method of calculation, implying that the method used by Tamagna et al. is the preferred one. That method, however, is the same as the one we have used, and the difference is only the semantics of reporting.

Our paper examined the effect of a 5000-rad dose on the clinical