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Standardization of Radioactive Iodine

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THE TECHNIQUES AND INSTRUMENTATION of standardization that are to be described here are those available generally in laboratories equipped for work with radioactive materials in biology and medicine. Problems that can be solved by specialized and more complicated methods in a purely physical laboratory will be discussed only in a general way; however, such measurements as can and should be performed by every user of radioactive materials, especially I–131, will be presented in more detail.

The standardization of a physical object involves first of all a description of the measurement procedure and a definition of the unit to be used. The two are, however, not necessarily independent of each other; and we usually are free to select more than one procedure and unit.

Let us consider a piece of steel. We can standardize it by weighing, and the unit which we will assign to it by this procedure may be the kilogram. As is true of every good physical unit, there are several well-known measurement procedures for comparing our piece of steel to the physically permanent standard kilogram. The "weight" is an adequate standardization result if we want to use the piece of steel as ballast in a ship. Should we want it for casting, however, weight will not be the information required; we shall need its volume, expressed, let us say, in ml. To measure this directly is rather more complicated than weighing; we should not be permitted to use density, since "density" implies that a volume measurement and weighing have been performed on the identical steel at least once previously. If we plan to use the piece of steel as an armor plate, we shall need a different standardization, its thickness in cm, which can be easily measured by a micrometer. The situation will become more involved if we are to use the steel as a gamma-ray absorber. The micrometer, which gives the thickness in cm, will be very useful as long as we use the same steel alloy. But if we use different steel alloys, or even different materials, we find that the simple absorption equation is complicated by a coefficient that is characteristic for every material and varies widely. We know from our experience that the variation of this coefficient is reduced by at least one order of magnitude if we standardize the thickness of absorbing materials in g/cm^2 instead of cm. Such standardization involves more complicated measurements than the simple use of a micrometer. Yet this is what we do, for reasons familiar to us all.

The purpose of this example is to recall the multitude of possible standardizations on the same physical object and to show 1) how availability and simplicity of measurement procedures may determine the selection of units, and 2) that, depending on the ultimate use and application of the information supplied by standardization, one system of units may be exchanged for another, for simplicity and convenience.

In working with short-lived radioactive isotopes, a gravimetric unit for standardization is practically impossible. One hundred μg of I-131, the smallest amount that can be weighed with reasonable precision, has, after filtration of beta radiation, a gamma radiation equal in ionization to about 15 g of radium. Such large amounts were undreamed of only a few years ago, and their handling is too hazardous for routine procedures. We had to work with very minute quantities, which could be detected and measured with the G-M tube.

The G-M tube indicates single radiation events associated with nuclear disintegrations. It seems natural, therefore, that, at a time when only small quantities of radioactive isotopes were available, most easily detected and measured by the G-M tube, a unit based on the disintegration rate was proposed and came into general use. This unit was derived from the curie—the amount of any nuclide of the radium family in secular equilibrium with 1 g of radium. It is hence derived from a gravimetric unit.

In selecting a disintegration rate unit for radioactive isotopes, it appeared natural at first to tie it in with radium measurements and to use as the unit a disintegration rate equal to the disintegration rate of one curie of radium. The disintegration rate of radium, however, is not known to better than about ½% accuracy. A number close to the experimental value was chosen, therefore, and was used in the definition: 1 millicurie of a radioactive isotope is the amount in which, at the time of measurement, 37 million disintegrations occur per second.

One of the objections raised against the use of the disintegration rate mc was the possibility of confusion with the radium mc. Condon and Curtiss have proposed the rutherford (rd), defined as 1 million disintegrations per second. I do not feel that the possibility of confusion is sufficiently serious to warrant the introduction of a new name and unit. Any standardization result always reads: "*x* units of *y* isotope." Whenever *y* is not radium, we know that disintegration rate is meant. It is scarcely worth while to differentiate the disintegration rate mc by a prefix as "isotope mc." The numerical simplicity of the "rutherford" is an even slighter advantage.

After this lengthy introduction we can approach our proper subject: standardization of radioiodine. Before we discuss how we can use the mc unit, let us look at Fig. 1, summarizing the results of standardizations performed in 70 different laboratories in this country on samples of equal content of I-131 (third intercomparison by the National Bureau of Standards). This offers quite a dismal picture. The standard deviation is about 30%; the range is from 43 to 180, about 1:4, almost an order of magnitude.

Obviously, standardization is not a simple procedure. Yet it is an extremely important one. If a worker at the upper end of the frequency plot reports a certain dosage for treatment of a given disease, and a worker at the lower end makes use of this dosage information, he will give four times the effective dose, will possibly exceed the therapeutic latitude, and will get deleterious results (permanent hypothyroidism, for instance, in treatment of Graves' disease).

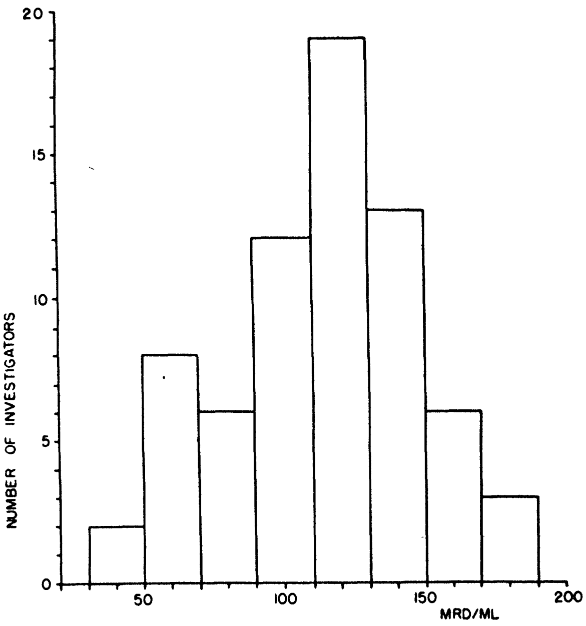

FIG. 1. Frequency distribution plot of standardization results by 70 laboratories (third intercomparison conducted by the National Bureau of Standards).

We can make some fairly good guesses at the reasons for this wide spread.

There are actually several factors involved, and for purposes of discussion we may differentiate three groups among the 70 laboratories: 1) those making their own primary measurements; 2) those comparing the counts from a standardization sample of a long-lived radioactive isotope with the counts from the I-131 sample to be standardized; and 3) those calibrating their measurement equipment with a sample of I-131 standardized by a laboratory of group 1 or 2.

The spread of the NBS intercomparison is obviously due to the discrepancies in the determinations of groups 1 and 2, on which are superimposed the errors of group 3. The discrepancies in the results of the workers in group 1 mirror the actual difficulties of absolute standardization in millicuries. Theoretically, the best and apparently the most direct method of disintegration rate determination is that of coincidence counting. However, this has the serious disadvantage that its correct use presupposes knowledge of the exact disintegration scheme. The disintegration scheme of I–131 that we had formerly assumed to be correct is now in doubt. This uncertainty makes the results of coincidence measurements doubtful.

A second method of absolute standardization in mc is based on the ionization produced by gamma radiation of I–131. If the old disintegration scheme were correct, and we could assume no internal conversion of the 80-kev photons, a 1-mc-sample of I–131 would produce 0.265 mr per hr at 1 m in air. The new disintegration scheme, accepting an incidence of a 650-kev gamma-ray transition, would increase this figure by at least 5%; and it would affect the results of coincidence measurements to an even higher degree.

The difference between NBS and Oak Ridge (coincidence measurements) on one hand, and the Memorial Hospital values (gamma ionization) on the other hand is at present about 20%. When the uncertainty in the disintegration scheme is overcome, we may expect this difference to disappear.

I shall not discuss the technical details of the absolute standardizations just described because they are normally beyond the scope of laboratories with a biological orientation. But I want to emphasize that we have encountered what I believe to be one fundamental difficulty involved in the use of the mc unit: in order to use it in the standardization of an isotope sample we need a considerable amount of information about the isotope's nuclear behavior, which we do not have for most isotopes.

Workers of group 2 have new difficulties, due to the different energies of the radiations of the long-lived reference standard and of I–131. The beta energy of RaD + E standard, for instance, is much higher than the beta energy of I–131. This brings about not only an increased error in the extrapolation for zero absorber, but introduces errors due to the difference in counter efficiency at different energies, and also differences in scattering. All this necessitates complicated corrections, with the possibility of a considerable cumulative error.

There is, at least theoretically, a solution for the method of group 2: the preparation of a long-lived isotope standard with a radiation of type and energy close to that of I–131. A 3.5-year-half-life isotope of thalium (Tl–206) disintegrates by beta emission of 0.87 Mev, which is close to the I–131 beta energy of 0.687 Mev. I–131 samples, compared with such a standard using suitable filters for gamma background correction, may give values requiring only small correction factors for the characteristics of the G-M tube and the material and geometry of the shelf setup. The ideal solution would be a mixture of long-lived isotopes, all of which have the same half-life, and which emit beta- and gamma-rays iso-energetic with I–131; however, such a mixture does not appear feasible.

An essential advantage of group 2 methods, apart from the difficulties and uncertainties which have been discussed, is the availability of a permanent reference standard which insures against short or long term fluctuations in the sensitivity of measuring equipment and against losing the calibration when replacing or changing such equipment.

We come now to group 3, which is our proper domain: standardization by use of instruments calibrated against a "known" I–131 sample. We have to keep in mind, of course, the errors and uncertainties in the measurements of group 1 or 2, who have supplied the sample.

As a first example, we may take the simplest situation which occurs in tracer work: we want to measure the excretion of I–131 after oral administration of a tracer dose. We will keep an aliquot of the administered solution as reference sample, and measure the excretion in urine against the known standard. This will not only eliminate automatically the decay factor, but it will also take care of long term instability of our G-M setup. There will be one very important precaution to be observed: there must be complete identity in the preparation and handling, and in the physical and geometrical counting setups of the reference standard and the measured sample. If we use dried samples in order to obtain maximum sensitivity, we risk variations not only in self-absorption but also in loss of I–131 from the two samples, due to differences in drying, pH, etc., between the standard and the urine samples. Loss of iodine is a serious source of error in working with dried samples. I suspect, for instance, that the lower values in Fig. 1 (intercomparison by the National Bureau of Standards) is due to the use of dried samples with the concomitant loss of active material.

It is simpler to eliminate this error by the use of liquid samples. G-M tube setups with adequate sensitivity have been devised for this work—concentric gamma counters (Marinelli), and mixed beta and gamma counting, using liquid samples with thin glass wall cylindrical G-M tubes or with bell type counters of sufficiently large diameter. When using liquid samples, the danger of losing some iodine is reduced, but not eliminated. Here the main factor is pH. In the preparation of samples from the alkaline I–131 solution supplied by Oak Ridge, we found it best to dilute with distilled water only, checking with indicator paper.

The usefulness of a known standardized I–131 sample for direct comparison ends in a few weeks because of radioactive decay. We might attempt to maintain the direct comparison method by preparing a secondary, tertiary, etc., 1–131 standard sample. But the errors will accumulate and in a few months we would expect a considerable drift from the original standard. We would, therefore, prefer to obtain a *permanent calibration* of our equipment on the basis of the original known sample. But the G-M tubes, which we hold in such a high esteem because of their sensitivity, are rather unreliable as far as the permanence of their calibration goes. Their counting efficiency is subject to many fluctuations, due to such factors as temperature, air pressure, and aging. To some extent, these fluctuations can be taken into account by frequent check (several times daily) against a radium source.

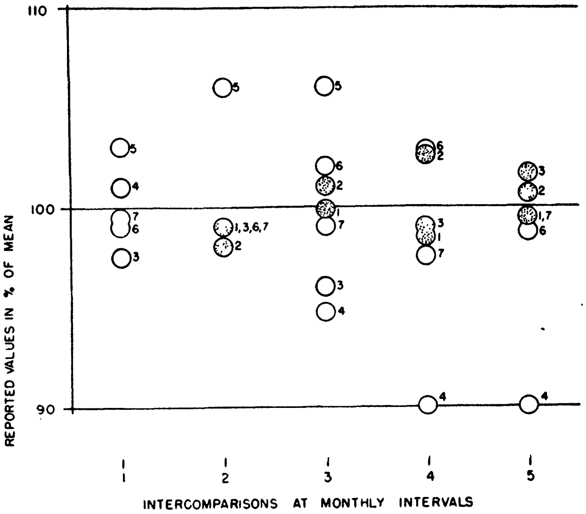

FIG. 2. Results of standardization by seven New York laboratories. Plain circles, G-M tube measurements; stippled circles, ionization chamber measurements.

When using such radium check, several points must be considered. Radium buttons of luminescent paint are unreliable because of the erratic loss of radon. Glass ampules with radium chloride solution, supplied by the NBS are adequate, but they are inconvenient to handle, and fragile. I have prepared sources with a few micrograms of radium by sealing radium paint in glass tubes and mounting the tubes in metal containers ¼ inch in diameter and 1 inch long. They are convenient to handle, since it is easy to place them in a reproducible position with respect to the counter by drilling a ¼-inch hole somewhere in the counter setup. The sources have proved satisfactory in our own and in two other laboratories.

The use of a radium check improves the constancy of the G-M tube calibration, but does not make it perfect or permanent; there is no reason to assume that the counting efficiency ratio of the G-M tube between the hard gamma radiation of radium and the softer gamma radiation and beta radiation of I–131 remains constant throughout the useful tube life. Using a radium check, one may expect a steady drift of the calibration. The use of a radium sample as a check is therefore an improvement, especially for short periods; but it is not a final solution. When a G-M tube is replaced, even by the same type of the same manufacturer, a new calibration against a "fresh" known I–131 sample is required.

Fig. 2 illustrates the degree of consistency in standardization practice that can be achieved between several independent laboratories using this method of calibrating equipment against a known sample.

Seven laboratories in New York City[1] have conducted monthly intercomparisons during the last five months. The radioiodine samples used in the original calibrations were standardized by the Memorial Hospital. In the third NBS intercomparison, we were all on the main peak of the frequency distribution plot (Fig. 1) and had a standard deviation of 3.5% among the seven laboratories. In Fig. 2, summarizing our local intercomparisons, the open circles represent G-M counting measurements. After the second intercomparison, Memorial Hospital corrected absorption extrapolations, and is now 10% below the mean based on the original Memorial values. The standardization results are within 5% of the mean. I believe, however, that without future recalibration these G-M values will drift apart.

I feel convinced that the solution of our problem is the replacement of the highly sensitive and somewhat temperamental G-M tube by a less sensitive but more rugged and reliable instrument for purposes of standardization, such as the ionization chamber.

The required sensitivity is dictated today, not by the available amounts of once scarce isotopes, but by health hazards in handling. Since it is relatively safe to handle a few hundred μc of I–131, the great sensitivity of the G-M tube is not required. The sensitivity of an ordinary thimble chamber, however, is not great enough.

Carl B. Braestrup has designed an ionization chamber of suitable sensitivity for use with I–131, which is illustrated in Fig. 3. This chamber can be used with any conventional electrometer of the Victoreen type. The I–131 sample is introduced into the chamber enclosed in a glass test tube. Correction factors for difference in volume of the sample are less than ½% up to 6 ml. The sensitivity is such that about 400 μc of

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[1] Columbia University, Radiological Research Laboratory, G. Failla (ionization measurements) and E. Quimby (G-M counting); Memorial Hospital and Sloan Kettering Institute, L. Marinelli; Montefiore Hospital, E. Oshry; Mount Sinai Hospital, S. Feitelberg; New York City Department of Hospitals, C. B. Braestrup; Veterans Administration Hospital, R. Yallow.

I–131 give the optimal discharge of 3/5ths of the Victoreen scale in 10 min.

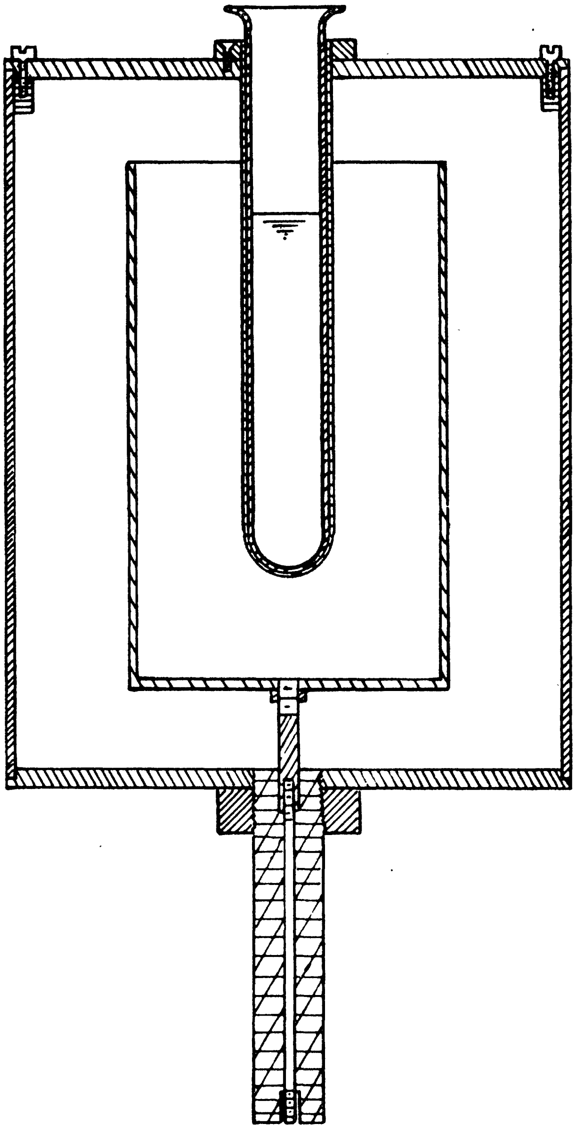

FIG. 3. Ionization chamber for gamma emitting isotopes, designed by Carl B. Braestrup. The chamber is made of brass, outside diameter 4 inches.

Another type of ionization chamber instrument has been designed by Failla; among other advantages it can also be used with pure beta emitters. However, it is rather expensive and not yet available commercially.

The essential advantage of ionization chambers is their simplicity, ruggedness and reproducibility. Once a Braestrup or Failla chamber is calibrated against a known radioiodine sample, it can be relied upon to give reproducible readings. Now the electrometer becomes the course of uncertainty, but we can eliminate this factor by checking against a radium source of 100 to 200 μg, which incidentally also compensates for variations due to air pressure and temperature changes.

The stippled circles in Fig. 2 are results of ionization chamber standardizations. They are within 3% of the mean. Radium checks, which have not been used yet for these measurements, may improve the consistency even further.

What precision in standardization do we need in biological work? The answer lies in the biological factors involved. For instance, the biological information for calculating dosage to the thyroid gland has a probable error of the order of 30%. We certainly do not want to have a physical error of similar magnitude superimposed on this. However, it would be unreasonable to require the errors in the standardization measurements to be less than an order of magnitude below the errors in the estimate of the biological factors. This means that we want the standardizations to be reliable within 3 to 5%, about what we expect in standardization of an X-ray machine.

If I may refer again to the intercomparison work of the New York laboratories, it appears that this precision can be achieved without undue difficulty, particularly when using ionization chambers. However, this pertains to relative and not to absolute measurements. We certainly do not believe that our New York mc comes within 5% of 37 million disintegrations per sec.

What is the ultimate purpose of the standardization information? It is two-fold: 1) to obtain a common denominator among all the workers, so that the experience of one group can be used by others, and so that the experience of all can be pooled in order to arrive at an empirically determined dosage; 2) to link the experience of internal radiation using radioiodine with the employment of other modalities of radiation therapy.

The present state of the art permits the accomplishment of the first purpose. I believe that one of the national agencies concerned with this work should initiate on a national scale a project similar to that undertaken by the New York laboratories at city level. In addition to supplying uniform standardized samples at regular intervals, such a project would also make available critique and advice on standardization practice to workers who find difficulties in achieving reproducible results. For this purpose it is irrelevant what I–131 mc unit is used. It should be possible, within a few months, to reduce the national spread to a standard deviation of at most 5%. We in New York will shift from our somewhat arbitrary but, we believe, consistent and reproducible "New York mc" to any value on which there is such national agreement.

The second purpose is linked with absolute measurements. An arbitrary mc dose does not permit us to use with confidence the factors necessary for calculating energy absorption in tissue (rep). Discrepancies in primary absolute measurements are considerable. We may have to wait until these discrepancies are resolved, and until the disintegration scheme of I–131 is thoroughly established. However, there is another solution. We could take, for instance, the New York mc and measure the energy emitted for such a unit of I–131. If such measurements were available (I believe that they are being made at present), we could calculate dosage in roentgen equivalents, and the mc with its inherent uncertainty would cancel out.

In this connection, I would like to recall to you Failla's suggestion for a unit of radioactive isotopes, which he calls "ruth," for Rutherford: one ruth is the amount of any radioactive isotope that emits ionizing radiation at the rate of one erg per sec. Since I believe that the ionization chamber will replace the G-M tube as a standardization instrument, it seems to me that the disintegration rate unit will lose its usefulness. It is not very practical to use a unit which implies disintegration rate measurements if the actual standardization practice measures the amount of ionization and does not count the number of ionizing events. But this is not the opportunity to recapitulate Failla's arguments, with which I personally agree. The main advantage of the ruth, I think, is that a unit based on energy emission furnishes more directly the information which we, as consumers of atomic energy, ultimately require.

I have attempted to present the material necessary for the evaluation of standardization procedures and for the accomplishment of reproducible comparison measurements. Our main effort in standardization work should be directed toward a uniform standardization, although this may be for the time being on the basis of a standard which is to some extent arbitrary. All of us can contribute to this limited objective.

The question of absolute standardization is the domain of a smaller group. The majority of us will have to wait for their results. But I hope that I may speak for this majority if I define what kind of result we need from absolute measurements: it is a result that will permit us to compute energy absorption of ionizing radiations of radioactive iodine in tissue.

Based on a paper presented at the Symposium on Radioactive Iodine held at Brookhaven National Laboratory, Upton, New York in July 1948.

Interstellar Polarization, Galactic Magnetic Fields, and Ferromagnetism

Lyman Spitzer, Jr., and John W. Tukey[1]

Princeton University

OBSERVATIONS by W. A. Hiltner (*5, 6*) and J. S. Hall (*4*) indicate that starlight becomes plane polarized in its passage through interstellar space. The effect increases with increasing distance, and according to Hall's data amounts to about 5 percent ($= e^{0.05}$) difference in intensity between the two plane-polarized components for a star whose color excess is 0.50 magnitude. Since the color excess is known to be about one-ninth the total absorption (which thus amounts to $(2.512)^{-4.5} = e^{-4.1}$ for such a star), the absorption must vary by somewhat more than one percent with the plane of polarization.

Such polarizing absorption would exist if needle-shaped particles, of dimensions comparable with a wavelength of visible light, were present in interstellar space, and were oriented by some force. The ratio of the scattering cross sections of such needles for the two planes of polarization would be appreciable; according to the theory by R. Gans (*3*), for a small prolate spheroid with a length twice its diameter, this ratio is 2.74 if the refractive index in the spheroid equals 2.5. Thus a relatively small number of needles could produce the observed effect.

Two difficulties seem to stand in the way of this explanation: the origin of the needles and their orientation. If we accept as a working hypothesis: (1) the existence of small ferromagnetic particles, which, existing as individual domains, are intensely magnetic; and (2) the existence of magnetic fields in interstellar space with systematic components as great as 10^{-5} gauss; then these difficulties disappear. The first of these suppositions appears reasonable from an exten-

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[1] The authors are indebted to Drs. John Turkevitch, John Wheeler, and Eugene P. Wigner for generous and helpful comments.