RADIOACTIVITY IN MAN

Whole Body Counting and Effects of Internal Gamma Ray-Emitting Radioisotopes

A Symposium

Held at the Vanderbilt University School of Medicine

Edited by

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PREFACE

IMMEDIATELY following publication of the first papers of the pioneering work of the Argonne National Laboratory group of Marinelli, Miller and Rose concerning the crystal human scintillation spectrometer and of the Los Alamos group of Anderson, Van Dilla and Langham describing the four pi liquid scintillation human counter it became apparent that here were powerful tools for medical research with capabilities not previously available by any means. Also, at once, was begun the exploration to determine the merits and demerits of the two types of instruments. From the first, it was evident that the liquid counter had higher efficiencies in terms of counts detected per gamma ray emitted in the body and an apparent inherent superiority in geometry. On the other hand, the high resolution of primary gamma rays which reach the detector of the crystal instrument makes possible sharper identification of isotopes and so offers an enhanced specificity. For most institutions, only one instrument is possible, consequently it became of great importance to thresh out in detail the assets and liabilities of each. There were added questions concerning specific medical applications, the facility with which studies can be done in seriously ill patients and questions of hazard and of down-time.

When the Vanderbilt symposium was planned, it was thought that enough information had accumulated to produce some answers in these areas. We determined that the program of the symposium should be tightly technical and that as much factual material as possible should be packed into a short period of time, providing only enough extra time for discussion so that obvious contradictions might be commented on—if not resolved. Soon, from all sides, we began to hear what has become almost a slogan in this field: "We have heard enough about hardware; let us get on with the uses of these machines." We are by no means convinced that this is a correct view. The hardware in question represents an investment of $50,000 to $100,000, requires a staff of not negligible proportions for effective operation, probably requires access to at least a small electronic data processing machine if full capabilities are to be realized, surely requires new construction or substantial modification of existing structures and is entirely capable of generating major administrative headaches. Also, it seemed to us that the observations made with an established instrument deserve reporting before the groups scientifically competent in the *biological* area concerned rather than before the heterogenous group of physicists, engineers and biophysicists concerned with its design and technical problems of its use. It seemed to us at that time—and it seems so to us much more strongly now that we have added experience—that not nearly enough attention has been given to the problems of calibration, the location of the isotope in question within the body, questions of absorption and the thorny matter of adequate reference standards. We were desirous, therefore, of focussing as sharply as we could upon these highly technical problems. The technique is so foreign to the understanding of the average physician or biologist and the instrument so formidable in its appearance and use that there is real danger the numbers which emanate from it will be accepted as oracular.

Further, it seemed to us that emphasis should be laid upon those things which can only be done with these instruments with lesser attention paid to those procedures which previously were possible but now are to a greater or lesser degree facilitated.

Finally, it seemed it would be begging the obvious question if we did not face the implications in areas into which only these instruments can take us; namely, the radiobiological, the medical, the sociological and the legal problems of small and increasing burdens of radioactivity in the human body.

These principles guided us in planning the program. So complete was the response to the initial round of invitations that we withdrew from presentation our own intended contributions to the program. Our only real sorrow at this was the elimination from the program of any special attention to the very great use of such instruments for training purposes. This phase of the use of these instruments has been scantily treated elsewhere and it is appropriate to say a word or two about this particular facet here.

These instruments not only generate data at a somewhat terrifying rate, but also they generate new technical problems almost as rapidly. The solution of these technical problems provides splendid training opportunities for graduate students, medical research fellows and postgraduate trainees of all kinds. Relatively short periods of data-taking produce amounts of information requiring substantial time for analysis and thus the instrument is "efficient" from the pedagogical point of view. The human body with each different isotope localizing and metabolizing in a different way presents challenging opportunities to work out the nuclear spectrometric physics involved, to exhibit ingenuity in the construction of physical and mathematical models upon which the data can be interpreted, to devise biological tricks which will bring out the wanted information and suppress the unwanted, to work out programs for efficient data processing—and all the while for the student to be surrounded by the vivid atmosphere of the interaction of modern physics, biology and medicine.

There are other practical questions to which insufficient attention has been given. A number of laboratories which have entered or which are entering this field have grossly underestimated the complexity of engaging in such work. There is a steady burden of electronic maintenance. This is no problem at a National Laboratory with sophisticated resources of this kind but multichannel pulse-height analyzers are not receptive to the "try shaking it" approach to repair. It is still the painful fact that the electronics maintenance will have to be done on instruments far short of "Mil-Specs" for reliability and often in spite of erroneous wiring diagrams and manuals which are skimpy to put it mildly. Continual pressure must be exerted to maintain a more than "surgical" grade of cleanliness; the battle against contamination must never cease. Some have advocated that these instruments should be "made available" to all comers in the institution but this cannot be done as simply as that. Aside from the opportunity to wreck the electronic components, especially the phototubes, by ill-advised control twiddlings, there is the much more serious matter of contamination. Until a worker has been thoroughly indoctrinated, it is impossible for him to understand the meaning of the level of sensitivity of these devices and the disastrous consequences of what must seem to him a very trivial spill. It is further unlikely that effective use can be made of the machine unless a serious training period has been experienced. Our philosophy is to make the services of the machine generally available, not its direct use. Thus we will make observations for interested investigators but only permit them direct access if they are willing to work through a thorough check-out with us. I do not wish to overdraw this phase. For certain uses, a few days of training is enough to learn the mere technique but to develop any understanding, sufficient, for example, to design and execute original studies, much more is needed and this against an adequate appropriate background of previous training.

Such a powerful tool is deserving of intensive use. Intensive use implies efficient use, efficient design of the experiment, efficient data processing and conscientious scheduling of studies. Wayward investigators cannot expect to wander in at random times with samples or subjects in tow and find the instrument idle. This is an especially distasteful fact to physicians for whom the only desired time is in the immediate few minutes following the thought to use it at all. In certain kinds of work the disappointment rate is high and alternative uses—for example, a sample counting backlog—ought to be maintained. Many low level applications of the crystal instrument require long counting periods such as 15 hrs. This is most effectively done on weekends. In the past we have made one such count every night but pressure of human studies has required us to put on an "evening shift" so only 10 hr. counts can now be done on weekday nights.

Evaluation of data requires a critical eye. Drift in energy per channel and zero shifts can propagate errors through analyses of observed spectra in unexpected ways. Careful and frequent standardization of the instrument with known sources is imperative if these drifts are to be detected and corrected. Otherwise, they may be undetectable in the final data. Harsh statistical scrutiny of all results is an absolute requirement. For example, when multichannel pulse-height analyzers make "cuts" between channels or groups of channels where the spectral curve is steep, rather large statistical fluctuations may occur which do not follow simple Poisson's distribution predictions based on total number of counts accumulated and Chi-square analysis will show improbable values. The analysis of these vagaries will tax the ingenuity of the investigator.

Some readers may be familiar with the extraordinary errors in thyroid iodine uptake measurements revealed by the ORINS study a few years ago. One set of data from a number of seemingly respectable laboratories revealed, for a manikin loaded to produce an apparent 60% uptake, observations from 30% to 130%, evidencing errors up to 100% both ways. These same laboratories performed well when asked to estimate the actual microcuries in a provided sample. Thus, when they made observations on standard-shaped samples in standard-shaped containers in standard geometry, they did well but when they made observations on "human beings" their results were sometimes bizarre in the extreme. With whole body counters the opportunity to be spectacularly wrong is infinitely greater than is the relatively simple thyroid procedure. We would be injudicious if we passed on too quickly to emphasis upon results. Rather, it would seem, we should emphasize rigorous investigation of the technical problems of the use of whole body counters and entertain a generous skepticism of "results" until we have better and more convincing published data on the literal details of technique.

Perhaps the most fascinating aspect of this work is the opportunity to measure with considerable precision the low levels of radioactivity present to some degree in everyone. Every citizen is a walking tracer experiment in cesium metabolism and it behooves us to understand it. When we follow the same individual from time to time, many of the uncertainties in calculation are diminished or absent and the opportunity to observe "change" is excellent even if we are somewhat skeptical of our "absolute" standardization. The most potassium deficient patient we have ever seen, at death's door for this reason, had an observed total body potassium quite "normal" by any criterion we have been able to devise or of which we have read. On the other hand our observed increase with therapy (about 20 Gm.) checked within a few per cent of the metabolism ward observations by direct intake-output measurement.

The cited case of our most potassium deficient patient whose total body potassium at the time of admission lay in the normal range by any known criterion is heightened when one scrutinizes the whole data. Thus the data of Anderson and Langham (with which we find ourselves at some important variance) are stated to have a coefficient of variation of ±7–14% about the means presented in their age versus grams per kilogram by sex presentation. An ordinary total body potassium might be 150 Gm. A coefficient of variation of ±7–14% would provide a range at the 95% confidence limit of ±21 to 42 Gm. This is obviously a nonuseful criterion for practical medical applications. Our most desperate case had an increment during recovery to apparent normalcy of 20 Gm. in a burden of 100 Gm. It is evident if the total body potassium measurement is to become useful as a clinical tool we will have to refine our ability to predict the normal.

In spite of all these uncertainties, the fact remains that determination of whole body potassium is one of the most exciting applications of whole body counting. Not the least of the difficulties in this field is that, as of the present moment, in the entire published medical literature there are only three adequate analyses of cadavers and these do not agree any too well among themselves as to the ordinary potassium content of the human body. Here is an area which we can recommend to a grimly determined investigator because only by adequate direct chemical analysis will the validity of our isotopic observations be confirmed.

The determination of whole body cesium presents a somewhat different problem. On the one hand, technically it is more difficult because the spectroanalysis requires not only the background and the radium subtraction but also the subtraction of a correct spectrum for potassium which cannot be perfectly known for all the different shapes and sizes of human beings. However, the dynamic range of the observed Cs^{137} levels in human beings is immensely larger than that of potassium. Our observations and those of many others indicate that the cesium burden of individuals may vary from person to person by a factor of three or possibly five. Here small errors in observation become much less important, and, as earlier mentioned, since the most fascinating thing is to follow the burden in a given individual, many of these uncertainties disappear.

One of our major enterprises at the present time is an attempt to characterize the cesium burden of a community, namely, Nashville, Tennessee, which we propose to do by studying the cesium burden of a very carefully drawn sample of this population. This sample has been organized on the basis of geographical distribution throughout the community of race, of sex, of economic status and the study has been guided by other appropriate sociological criteria. Then, following this analysis, a random number technique was employed to select households. All of the members of these particular households are in the process of being assayed for their cesium burden. If we are able to persuade a substantial fraction of this sample to submit to the counting process, we should be able to generalize our observations to characterize the burden of the citizens of our city.

These proceedings are presented, then, gratefully acknowledging the genius and ingenuity of the physicists, the engineers and the biophysicists and the competence and dedication of public and private collaborators in medical research.

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John H. Stambaugh, Vice-Chancellor, Vanderbilt University;

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G. R. M.

* Dr. Goodpasture died on September 20, 1960.

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