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TO : Louis Rosen, MP-DO

DATE: 3 November 1970

FROM : Dick Hutson, MP-7, and Arvid Lundy, MP-1 A.L. R.H. 712986

SUBJECT: MEDICAL USE OF MUON-ACTIVATION ANALYSIS

SYMBOL : MP-1

This is a report on our investigation of the subject technique to date.

Several weeks ago, Wright Langham sent us a reprint of an ICRP report on elemental composition of the body. With this data, we calculated capture probabilities in tissue for the fifteen most common elements, using the Fermi-Teller "Z" law. This data was discussed with Herb Anderson when he was here and he indicated that it was probably feasible to assay at least a few elements, but he felt that clinical justification was needed before proceeding with any sort of experiment. One of us, Lundy, visited Anderson in Chicago at the time of the Proton Linac Conference and looked over the muon experiment area at the cyclotron. It appears that running an experiment there would be reasonably easy. Anderson mentioned that Max Boone had written him, stressing his interest in this. Anderson also restated his strong feelings that we need an M.D. involved in this from the start if we are going to do anything, and, that he needs some possible clinical justification for the work, in order to justify getting cyclotron time.

We then contacted numerous people, mostly by telephone, concerning possible clinical applications. These people included:

- Dr. Max Boone, University of Wisconsin
- Dr. C. R. Key, Pathology Dept., University of New Mexico
- Dr. Lawrence Lanzl, Argonne Cancer Hospital
- Dr. John Laughlin, Sloan-Kettering Institute
- Dr. Sam Seal, Radiotherapist, Sloan-Kettering Institute
- Miss Mary Lou Meurk, Physicist at Zellerbach Saroni Tumore Institute, San Francisco
- Dr. Wil Nelp, University of Washington (M.D. working with neutron activation)
- Dr. Peter Wootton, Physicist at University of Washington
- Dr. Henry Schroeder, Dartmouth (Physiologist in charge of the Trace Elements Laboratory)
- Dr. Jon Shoop, Radiology Department, University of New Mexico
- Dr. C. F. Tessner, M. D. Anderson Hospital and Tumor Institute, Pathology Dept., Houston, Texas

While several ideas were obtained from these people, the people seemed either relatively uninterested, did not have specific ideas, or their ideas did not seem technically feasible. A brief literature search was also made, primarily for information on human neutron activation work. About a dozen papers were found relative to this area.

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It then seemed that better information was needed on what elements one might assay in tissue before looking further for clinical justification. In connection with this, a literature search was made for experimental data on capture probabilities, mesic X-ray energies, and relative yields of the various lines. Over 35 papers were found in these areas. A draft of a new ICRP report concerning elemental composition of humans was obtained from Dr. Walter Snyder at Oak Ridge. Using this data, a chart (attached) listing the X-ray yield per captured muon in tissue of each of the K_α, K_β, K_ν, and L lines was prepared and also a line spectra graph showing X-ray energies and anticipated yield. (The Fermi-Teller "Z" law was used to estimate capture probabilities, although considerable experimental data is available, indicating that this does not hold, except in metals.) We then contacted John Balagna in J-11 concerning information on which lines would be separable. He is in the process of checking this out by computer summing individual spectra, taken on a 35 cc Ge(Li) detector system, from individual gamma-emitting nuclides, corresponding in energy to the expected muonic X-ray lines and appropriately scaled in intensity. The resultant composite spectra should be quite similar to what one would get from tissue being irradiated with muons. The results of this should be available next week.

Bruce Goplen, MP-3, wrote a computer program for generating theoretical muonic X-ray spectra from tissue, as seen by a typical Ge(Li) detector. Unfortunately, the line intensities calculated do not agree with experimental data and a further problem is that none of us knows enough about Ge(Li) detectors to feel much confidence in the model chosen to represent the detector. The approach that J-11 is taking seems more useful at present.

One of us, Lundy, gave a brief talk at the Biomedical Users Meeting on Saturday concerning mu-activation technique. In this talk, he mentioned the following possible clinical applications:

1. Assessment of calcium mineral content in bone. (This almost certainly can be done and at lower dose to the patient than with neutron activation. However, it also is being done very effectively with X-ray absorption techniques, as developed by John Cameron at Wisconsin and, therefore, is of questionable value.)

2. Nitrogen quantification in certain organs because nitrogen is basic to protein metabolism and, therefore, probably varies in certain disease states. (More data on this is needed.)

3. Intracellular sodium-potassium balance studies. When cell damage occurs, this balance shifts and serum studies of it do not seem to reflect the intracellular changes. Sodium probably cannot be assessed, but potassium might be. Could one scan the heart, in a heart-attack victim, with a muon beam, and obtain a plot of potassium distribution? Preliminary estimates of the required radiation dose to the patient indicate it to be well within the usual diagnostic radiology limits.

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4. Magnesium studies in various disease states. (This was mentioned by several people contacted, although just what its significance is, is not clear to us.)

5. Zinc studies in the prostate gland for possible correlation with prostate cancer. (This also was mentioned by several people, although one pointed out that considerable work has been done on this with surgically-removed tissue and the correlation has not been proven.)

6. Determination of carbon concentration in tumours during fractionated radiation therapy. In the paper by Spring and Väyrynen (attached), periodic changes as high as ±20% are reported. If the explanation proposed by them is true, this effect can be used to measure the amount of cell cycle synchronization in the tumour, due to fractionated therapy and also the cell cycle period. This could be very valuable information for the radiation therapist. (Pi-activation might be used during radiation therapy.)

John Cameron, Professor of Physics and Radiology at the University of Wisconsin, indicated a great deal of interest in the mu-activation analysis technique. He suggested that we visit the University of Wisconsin to talk further about possible applications and said he would arrange for a seminar there, if we so desired. He said he felt that this technique was potentially more important medically than pion radiation therapy. Dr. Henry Schroeder at Dartmouth also indicated considerable interest and said he would be interested in consulting on such a project on a mail or telephone basis (he is [redacted] and cannot readily travel). Dr. Wil Nelp at the University of Washington (a leader in neutron activation work) suggested that when we know better what elements we might assay, we send someone (preferably a clinician) to one of their small informal discussion meetings on the clinical uses of neutron activation analysis. He indicated that they periodically invite a few people from around the country for a day of idea exchange.

At this point, there are still several complicating factors which need further study. Among them are:

1. Lack of knowledge of the muon capture probability for the atoms of a given element when the element occurs within a complex organic molecule.*

2. The problem of determining how many muons have stopped in a given mass of tissue of a particular type--i.e., in the liver, in a given bone, etc.

3. How to correct for X-ray self-absorption effects in tissue. (A similar problem exists in neutron activation analysis, of course.)

*Also, lack of knowledge of the relative X-ray line yields for a given element as a function of chemical bonding.

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4. Evaluation of the radiation dose delivered to tissue by the muons, mu-mesic X rays, and nuclear interaction products.

5. Lack of knowledge of normal variation of elemental tissue composition.

6. Uncertainties in knowledge of X-ray yields of different transistions in various atoms.

At this point, it seems well worthwhile to continue work to define the potential of this technique, but it appears that full development of it, for clinical usage, could require the work of several people for several years. We plan to write an internal memo on it within a few weeks after we evaluate the J-11 data and talk further with clinicians concerning which of the feasible elements are of most interest.

Distribution:
T. Putnam, R. Gore, MP-1
B. Goplin, MP-3
L. Agnew, MP-7
W. Langham, H-4
David Groce, J.R.B. Associates
M. Stewart, M. D., LAMC
J. Balagna, J-11

Enclosures:

1. Gross and Elemental Content of Standard Man.
2. Chart of Muonic X Rays from Standard Man.
3. Spring and Väyrynen, "Measurement of Changes in the Oxygen and Carbon Concentration of Tissues during Fractionated High Energy X-ray Treatment."
4. Danielson and Steinnes, "A Study of Some Selected Trace Elements in Normal and Cancerous Tissue by Neutron Activation Analysis."
5. Palmer, Nelp, Murano, and Rich, "The Feasibility of in vivo Neutron Activation Analysis of Total Body Calcium and Other Elements of Body Composition."
6. Daniel, Kock, Poelz, Schmitt, Tauscher, Backenstoss, and Charalambus, "Condensed-State Effects in Muonic X-ray Spectra."
7. Zinov, Konin, and Mukhin, "Transfer of a Negative Muon from a Proton to Carbon."
8. Baijal, Diaz, Kaplan, and Pyle, "Atomic Capture of μ^- Mesons in in Chemical Compounds."
9. Grin and Kunselman, "Solid-State Effects in Pionic Atoms."
10. Budyashov, Ermolov, Zinov, Kronin, and Mukhin, "Structure of K Series of Argon in Atomic Capture of Negative Muons in the Pure Gas and in a Mixture with Hydrogen."
11. Zinov, Konin, Mukhin, and Polyakova, "Investigation of K-series Structure in Atomic Capture of Negative Muons in Chemical Compounds."
12. Zinov, Konin, and Mukhin, "Atomic Capture of Negative Muons in Chemical Compounds."
13. Budyashov, Zinov, Konin, and Mukhin, "Muon Capture in Gas Mixtures."
14. Ponomarev and Prokoshkin, "Large Mesomolecules."

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MUONIC X-RAYS FROM STANDARD MAN (Most Common Elements Considered)

Element	Z	% of Total Body[1]	% Capture Probability[2]	K_α Energy[3]	K_α Yield[3,4]	K_β Energy[3]	K_β Yield[3,4]	K_ν Energy[3]	K_ν Yield[3,4]	L_α Energy[3]	L_α Yield[3,4]
1. Oxygen (O)	8	61	68.0	133	68.0	-	-	-	-	24.0	31.4
2. Carbon (C)	6	23	25.6	75.5	25.6	-	-	-	-	13.9	6.17
3. Hydrogen (H)	1	10	-	-	-	-	-	-	-	-	-
4. Nitrogen (N)	7	2.6	2.90	102	2.90	-	-	-	-	18.9	1.03
5. Calcium (Ca)	20	1.4	1.56	786	1.29	946	.105	1034	.167	158	1.22
6. Phosphorus (P)	15	1.1	1.19	458	.952	523	.095	548	.143	88.0	.898
7. Sulfur (S)	16	0.20	.222	522	.176	618	.018	666	.028	100	.170
8. Potassium (K)	19	0.20	.217	713	.182	851	.012	936	.022	140	.170
9. Sodium (Na)	11	0.14	.150	250	0.150	-	-	-	-	-	-
10. Chlorine (Cl)	17	0.12	.128	583	0.102	683	.010	738	.015	113	.0989
11. Magnesium (Mg)	12	0.027	.0297	296	.0297	-	-	-	-	-	-
12. Silicon (Si)	14	0.026	.0289	400	.0231	450	.0023	460	.0035	76.6	.0214
13. Iron (Fe)	26	0.006	.00622	1262	.00439	1531	.00053	1706	.00130	264	.00494
14. Fluorine (F)	9	0.0037	.00391	168	.00391	-	-	-	-	-	-
15. Zinc (Zn)	30	0.0033	.00338	1615	.00270	1960	.00027	2195	.00041	356	.00269
16. Rubidium (Rb)	37	0.00046	.000444	2245	.000355	2725	.000036	3045	.000053	545	.000355
17. Strontium (Sr)	38	0.00046	.000445	2325	.000356	2825	.000036	3165	.000053	576	.000356
18. Bromine (Br)	35	0.00029	.000283	2058	.000226	2498	.000023	2798	.000034	488	.000226
19. Lead (Pb)	82	0.00017	.000150	4763	.000150	-	-	-	-	2451	.000120
20. Copper (Cu)	29	0.00010	.000102	1510	.0000728	1838	.0000072	2054	.000021	332	.0000813

1. % by weight (total body) per I. H. Tipton, "GROSS AND ELEMENTAL CONTENT OF REFERENCE MAN".

2. Calculated per Fermi-Teller "Z" Law.

3. The energies (in KeV) and relative yields of the various lines for a given element were obtained by surveying a large number of papers reporting experimental results. In some cases, no reference could be found and interpolation was used for energy and both interpolation and extrapolation for yield. It is difficult to estimate errors in this data. The yield data is less accurate than the energy data.

4. Yield is stated in terms of % per body captured muon. No allowance was made for tissue self-absorption or decreased mesic X-ray yield in low Z elements. (Some papers show this later effect, probably due to Auger transitions, to not exceed a few percent in the elements of interest here.)

A. Lundy, 10/27/70

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