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**Meeting of the
Bio-Medical Program Directors
of the
United States
Atomic Energy Commission**

APRIL 24-25, 1961

OPERATED BY THE UNIVERSITY OF CHICAGO
UNDER
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F O R E W O R D

In 1948 the U. S. Atomic Energy Commission approved the establishment of a cancer research hospital with appropriate laboratory facilities at the University of Chicago. It was intended that this hospital be administered by the Medical School and Clinics of the University, and that its facilities be available to qualified investigators. After nearly three and one-half years of building, the first patient was admitted on January 10, 1953, and the formal opening date of the hospital was March 10, 1953.

The purpose and program of the hospital are directed toward the exploitation of high energy sources for the treatment of malignancies, the study of the biological effects of radiation, the use of radioisotopes as tracers in the study of normal and disease states, and in the diagnosis and therapy of disease. The scientific program is correlated in general with that of the Division of the Biological Sciences and the University of Chicago Clinics, of which the Argonne Cancer Research Hospital is, in fact, a part. Close relations are also maintained with the Argonne National Laboratory at Argonne, Illinois.

From the beginning the staff of the ACRH has encouraged participation in its research program by graduate and undergraduate medical students and advanced students in the biological sciences at the University of Chicago. It has also taken an active part in various research investigations of general interest with University faculty members in the Life and Physical Sciences, and this inter-disciplinary effort has proved of great value to the ACRH program. Student participation and faculty collaboration have also made possible the training of large numbers of undergraduate and graduate students (as well as faculty) in the use of radioisotopes in research, diagnosis and treatment of various disease states.

Argonne Cancer Research Hospital has eight floors, with a total area of 102,500 square feet. Two floors with 58 beds are devoted to clinical research. The remaining six floors house high energy radiation equipment, electronic and machine shops, an animal farm, and conventional research laboratories. The staff is composed of 58 scientists, 136 technicians, nurses, and non-technical laboratory personnel, many of whom are paid in part by the University. Since the University clinical departments assume care of the patients at the ACRH, any part of a staff member's time devoted to professional care as distinguished from research is paid for by the University and does not feature in the ACRH budget. This accounts for the fact that the scientific staff totals 58, while the actual number of scientific man years devoted to the research program is 49.

H. Stanley Bennett, M.D.
Dean
Division of the Biological Sciences
University of Chicago

PROGRAM†

Monday, April 24, 1961

Morning Session

- 9:30 Introductory Remarks
H. Stanley Bennett
Dean of Biological Sciences, University of
Chicago
- 9:45 Radioisotopes Therapy in Diagnosis
P. V. Harper, Jr. (pp. 1-9)
- 10:15 Studies on Yttrium-90 Hypophysectomy
R. D. Moseley, Jr. (pp. 1,3)
- 10:45 INTERMISSION
- 11:00 Studies of the Metabolism and Effects of the
Alkaline Earth Metals in Man
R. J. Hasterlik (pp. 10-16)
- 11:30 The Use of C¹⁴-Labeled Compounds in Clinical
Research
G. V. LeRoy (pp. 17-30)
- 12:15 The Specificity and Effectiveness of Anti-
Tumor Gamma Globulin
R. W. Wissler (p. 32)
- 12:45 LUNCH

Afternoon Session

- 2:00 *Wissler*
et al Effect of X-Irradiation on the Metabolism of
Glycogen in the Skin
S. Rothman (p. 37)
- 2:30 Radiation Damage to the Stem Cell
L. O. Jacobson (p. 38)
- 3:00 X-ray Studies on Transplantation Immunity
E. L. Simmons (pp. 44-48)
- 3:30 INTERMISSION

† Page numbers locate abstract and lists of senior authors and co-authors.

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- 3:45 Steroid Metabolites: Their Physiologic and Pharmacologic Significance
A. Kappas (pp. 60-62)
- 4:25 The Metabolic Effect of Progesterone in the Human Being
R. L. Landau (p. 63)
- 5:00 The Effect of Erythrocyte Stromata on Erythrocyte Enzymes
P. E. Carson
- 6:00 DINNER for Visitors and Participants at the Quadrangle Club, 1155 East 57th Street

Tuesday, April 25, 1961

Morning Session

- 9:00 The Design and Characteristics of the Chicago Linear Accelerator
L. S. Skaggs (p. 67)
- 9:25 Depth Dose and RBE Studies with High Energy Radiation
L. H. Lanzl (pp. 70-73)
- 9:55 The Therapeutic Use of High Energy Radiation
J. W. J. Carpender (p. 76)
- 10:20 Studies on Radiation Sensitizers
M. L. Griem (p. 80)
- 10:50 INTERMISSION
- 11:00 The Biosynthesis of Ribonucleic Acid
S. B. Weiss (p. 85)
- 11:30 *2⁰¹⁻⁶* Cytoplasmic Synthesis of Ribonucleic Acid
E. Goldwasser (pp. 87,89)
- 11:55 The Metabolism of Uric Acid and Some Clinical Aspects of its Derangement
L. B. Sprensen (pp. 96-99)
- 12:25 Phospho-Protein Metabolism
M. Rabinowitz (p. 92)
- 1:00 LUNCH

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Tuesday Afternoon

2:00

Executive Session
Presiding:
Dr. Charles L. Durham, Director
Division of Biology and Medicine
U. S. Atomic Energy Commission

Informal tour of hospital and visits to individual laboratories

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ARGONNE CANCER RESEARCH HOSPITAL

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ABSTRACTS

The following collection of abstracts includes summaries of work in progress, unpublished work, or work that has only recently appeared in the open literature. Those abstracts marked with an asterisk (*) have not yet been formally presented to the AEC Washington Office of the Division of Biology and Medicine. It is therefore requested that this volume be treated as a privileged communication not to be quoted in reference - EDITOR.

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Abstracts edited and compiled by Margot Doyle and Frances J. Skozen

METABOLIC STUDIES OF ALKALINE EARTH METALS

Metabolism of Strontium and Calcium in the Human

R. J. Hasterlik

The possibility of extensive environmental contamination by strontium-90 and the present actuality of some degree of contamination has resulted in heightened interest in the metabolism of this element by the mammal. Considerable species variation in retention has been found, as well as differences in the primary routes of excretion. This species variation is sufficient to make animal studies of doubtful predictive value regarding human metabolism of strontium.

Our investigation was designed to study the fate of intravenously administered tracer amounts of strontium-85, which is an ideal isotope for metabolic balance studies. Its half life of 65 days is sufficiently long to allow adequate long-term studies, and its gamma ray of 0.51 MEV allows determination of total-body burdens by external counting techniques. Carrier-free tracer amounts of $\text{Sr}^{85}\text{Cl}_2$, in doses from 26 to 40 μc , were administered intravenously (to seven adult subjects, six male and one female). Multiple serum specimens were withdrawn during the 30 hours after injection, then at longer intervals during the ensuing 24 days. All urine and stool specimens were collected and counted for strontium-85 activity. Four hours after injection, and before the patient had defecated or urinated, the total-body gamma activity was measured, and this activity was considered to represent 100 per cent of the strontium-85 administered for estimation of subsequent body burden levels. Patients were measured with the mid-plane of the body on an arc one meter distant from a 1-1/2" x 2" thallium activated sodium iodide crystal. Pulses from the photomultiplier were fed into a 256 channel pulse height analyzer and strontium-85 determined from the 510 KV photopeak which in this instance represented the sum of seven channels.

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Blood serum levels for strontium-85 showed a rate of disappearance tending to conform to that of calcium. At 30 hours, less than half the activity of the serum at three minutes remained. This rapid serum clearance phase is interpreted to represent skeletal uptake of the element. The subsequent more gradual rate of disappearance represents excretion via the gut and kidney, with serum and skeletal strontium in an equilibrium favoring the latter. Though this general pattern was seen in all subjects, correlations between serum activity, excretion rates and body retention of strontium could not be made.

As with radium, we chose the term "Body burden" to describe the gamma activity emitted following strontium-85 administration. In six subjects, retention of strontium varied from 22 per cent to 60 per cent 24 days after injection. M.W., a post-menopausal woman with moderate osteoporosis retained 60 per cent of the strontium during the study, and a 66-year-old male with multiple myeloma retained 53 per cent. These subjects, both with skeletal deossification, retained considerably more than four subjects without skeletal disease. Two males in the sixty-year-age group retained approximately 40 per cent. Another male retained 35 per cent of the administered strontium, and the least retention was 20 per cent at 24 days. Although no conclusions can be drawn from these limited data, it would seem that strontium is retained with greater avidity where there is deossification of the skeleton.

The predominant routes of excretion of strontium was variable. Of the six balance studies performed, two showed definite preponderance of urinary excretion, two excreted strontium primarily via the gut and two had approximately equal fractions in the urine and feces. Urinary excretion exceeded fecal in two subjects without known skeletal disease; there was predominance of fecal excretion in two subjects with skeletal deossification who were the subjects showing the greatest retention of strontium.

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We have as yet no adequate explanation for the rather marked difference in methods of excretion. McCance and Widdowson conclude from a short-term study that the element is primarily excreted via the kidney. This conclusion has been supported by Laszlo and Spencer, using carrier-free strontium-85. Spencer believes that a parallel exists between urinary calcium and strontium excretion, that is, that subjects who for some reason excrete low urinary calcium excrete relatively more strontium via the gut. Though urinary calcium determinations were not carried out on our two subjects with predominantly fecal excretion of strontium, studies of renal function were normal in both subjects. The gamma globulin was increased in patient L.T., who had multiple myeloma and bony lesions. Our results tend to support those of the few other studies on strontium-85 metabolism that report primary excretion via the kidney. We are aware of no report of excretion primarily via the gut in humans, although such is the case in mice. The role that skeletal deossification might have played in altering pathways of excretion is difficult to conjecture upon. It is tempting to speculate that strontium was retained longer in these subjects because of decreased renal excretion. It is, however, possible that skeletal retention kept serum strontium at a level insufficient for renal tubular secretion, although serum strontium values do not support this suggestion. We feel that the most likely cause of strontium retention in these subjects is replacement of skeletal calcium by strontium, a phenomenon consistent with Shorr's observation of metabolism of strontium in osteoporosis.

It was our good fortune to have available for study a patient with metastatic parathyroid carcinoma. A total of 50 μ c strontium⁸⁵ was administered intravenously, and total-body counting was performed over a 238-day period thereafter. His serum calcium was elevated throughout this period, as were the urinary calcium and serum alkaline phosphatase. He was in chronic

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negative calcium balance, improved somewhat in the latter stages of his course by one or more procedures to be mentioned. Twenty-four days post-injection, 86 per cent of the administered dose was still retained. The higher initial dose and the striking retention made accurate determinations possible until shortly before his death. Ninety-six days post-injection, total-body burden was calculated as 73 per cent of the administered strontium. In an effort to afford palliation from the carcinomatous condition, a hypophysectomy by transnasal yttrium-90 bead implantation in the sella turcica was performed on the 144th day post-strontium-85 injection. Whether by one or all of the efforts to alter the hormonal milieu, serum and urinary calcium levels were reduced, and a significant alteration in the negative calcium balance toward normal was demonstrated. It has been speculated that the testosterone was most probably responsible for the beneficial effect on calcium metabolism.

It is interesting to note that strontium excretion proceeded in association with high, though falling, urinary calcium levels. Unfortunately, the very low levels of strontium-85 in the excreta made these calculations impossible. Although to a much greater extent, this subject followed the pattern of increased strontium retention seen in the previously described subjects with skeletal deossification. Whether this marked affinity was secondary to the more severe skeletal disease or was secondary to the functioning parathyroid tumor is a matter for speculation.

In the past few months we have begun studies on the metabolism of calcium in the human using the 4.7 day half-life calcium-47. Patients are counted in the ACRH low-level total-body counting facility and it has been estimated that a single 20 μ c dose of calcium-47 can be followed for two to three months following administration.

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Radium Toxicity Studies

R. J. Hasterlik

The ACRH - ANL group has completed clinical and radiographic studies of 221 former dial painters. In addition, about ten others have been studied, the data for which are not included in this report. Determination of body burden of Ra²²⁶ is done by C. E. Miller at the Argonne National Laboratory and radiographic interpretation carried out by the author and Dr. A. J. Finkel of ANL. The criteria for grading of the frequency and severity of bone lesions recognizable on radiography developed by this group have also been adopted for use by the MIT and New Jersey Radium Study Groups.

The individuals reported on in this study represent a group better adapted for evaluation of the long-term effects of radium deposition, than those described in a previous ANL publication because this earlier study was heavily weighted with persons first coming to the group because of the presence of orthopedic and other difficulties secondary to their body burden of radium. The present study deals with persons selected almost entirely because of a history of former employment in Illinois as radium dial painters. Of the 221 persons measured, 67 carried a body burden of Ra²²⁶ at or above the permissible level of 10^{-7} curies. Of these 67, 64 have had complete radiographic studies. Of the remaining 154 carrying a body burden less than 10^{-9} to 10^{-7} curies, 129 have been completely studied.

It will be noted that only two of these patients contained an admixture of Ra²²⁶ and Ra²²⁸. This scientifically fortunate circumstance permits an intercomparison between the severity of bone lesions seen in our essentially "pure" Ra²²⁶ group with those seen in the mixed Ra²²⁶, Ra²²⁸, and Th²²⁸ containing patients of the MIT and New Jersey groups.

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Frequency and Severity of Bone Lesions as Related to Radium Burden

Body Content μc	Number		Radiographic changes in skeleton attributable to radium deposition					
	Measured	X-ray	None	Minimal	Mild	Moderate	Advanced	(Malignant)
< 0.001	23	18	15	3	0	0	0	0
0.001 - 0.0031	7	6	6	0	0	0	0	0
0.0032 - 0.0099	26	19	19	0	0	0	0	0
0.01 - 0.031	65	57	53	3	1	0	0	0
0.032 - 0.099	33	29	23	5	0	1**	0	0
0.10 - 0.316	26	26	17	4	3	2*	0	0
0.32 - 0.99	18	17	1	4	5	5	2	(1)
1.0 - 3.16	20	19	0	1	4	4	10	(4)
3.2 - 5.49	<u>3</u>	<u>2</u>	0	0	0	1	2***	(0)
	221	193						

* MsTh present in each case

** Final diagnosis deferred; further studies pending

*** Based on films taken elsewhere in one case

All radiographs are read "blind". Each of the two persons analyzing the films is unaware of the circumstances of employment or the body burden of the individual under study. After an objective analysis of the films each reviewer independently makes an estimate of the radium burden based on his experience. Lesions charted as "minimal" include those often seen as a phenomenon of aging and little reliance can be placed on this particular class of lesion as a unique indicator of radium-induced damage to bone. It will be noted that one individual carrying between 10^{-8} and 3.1×10^{-8} C demonstrated bony lesions characterized as "mild". Above 10^{-7} C of Ra^{226} the number and severity of bony lesions increases markedly in relationship to ascending burdens of radium. No malignant tumors have been seen at body burdens of less than 8×10^{-7} C.

The osteosarcomata seen in radium-bearing persons have been well described. Less well known are the tumors arising in the tissues derived from the primitive pharynx which line the paranasal sinuses and mastoid air cell in the adult. We have studied as our patients (or have had the opportunity of studying radiographs and tissues of patients of other physicians) eight persons bearing these very rare tumors who also carried a body burden of radium. The types of tumor and the site of origin follow.

<u>Body Burden in C</u>	<u>Tumor</u>	<u>Site of Origin</u>	<u># of Patients</u>
1.4×10^{-6}	Epidermoid Carcinoma	Mastoid Air Cells	5 patients
1.4×10^{-6}			
4.7×10^{-6}			
2.5×10^{-6}	Epidermoid Ca. + Fibrosarcoma	Mastoid Air Cells	1 patient
Unknown	Liposarcoma	Maxillary Sinus	1 patient
2.6×10^{-6}	Undetermined Tumor	Sphenoid or Ethmoid Sinus	1 patient

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