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THERAPEUTIC TRIALS OF RADIOGALLIUM ( $Ga^{72}$ )

A Report of Four Cases

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RESULTS of studies of the distribution of gallium and its excretion pattern and toxicity in experimental animals have been reported by Dudley and associates<sup>1</sup> and by King and others.<sup>2</sup> Clinical trials in the radioactive use of the isotope  $Ga^{72}$  as a possible diagnostic agent for the early localization of malignancies involving bone have been reported by Mulry and Dudley<sup>3</sup> and by King and associates.<sup>2c</sup> Brucer and associates<sup>4</sup> have reported upon the results of a therapeutic trial of  $Ga^{72}$ .

Radiogallium,  ${}_{31}Ga^{72}$ , is produced by neutron bombardment of natural gallium ( $Ga^{69}$ ,  $Ga^{71}$ ) with thermal neutrons, resulting in a mixture of radioactive gallium ( $Ga^{70}$  and  $Ga^{72}$ ).  $Ga^{70}$  has a half life of 20 minutes and plays no important biological role.  $Ga^{72}$  has a half life of 14.3 hours and is a beta and gamma emitter. The mean effective beta energy equals 0.45 mev, while the gamma emission is 1.59 times as energetic as the gamma emission of a similar quantity (millicurie) of radium. The

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tissue dose (beta and gamma) for human beings is approximately 85 r per millicurie per gram of tissue for total disintegration.

Gallium has been shown to be deposited at a rather rapid rate in areas having osteoblastic activity, such as the epiphysis in young animals, healing fractures, osteogenic sarcomas, and certain metastatic lesions involving bone.<sup>5</sup> Gallium was found to be moderately toxic; on a basis of 1 mg. of gallium per kilogram of body weight, the toxic effects were more pronounced on larger animals than on smaller species.<sup>1c</sup> In experimental animals, the limiting condition for the study of the radiation effects of Ga<sup>72</sup> is the toxicity of the carrier gallium.

Radiogallium (Ga<sup>72</sup>) citrate in tracer amounts (300 to 800 mc.) has been used clinically for study of its localization in malignant bone lesions by means of externally positioned Geiger tubes.<sup>6</sup> The findings indicated that gallium is concentrated in some metastatic lesions of the osteoblastic type. Its usefulness as a diagnostic agent is still being studied.

A study of 21 patients treated with a therapeutic course of radiogallium (Ga<sup>72</sup>) citrate has been reported. The results indicated that in order to approximate the tissue level of radiation necessary for cancericidal effect, a toxic dose of the carrier gallium was necessary. Consequently, use of Ga<sup>72</sup> was considered ineffective as a therapeutic measure in this series of cases.<sup>4</sup>

This report presents the clinical, x-ray, and autopsy findings on four patients treated with repeated doses of radiogallium (Ga<sup>72</sup>) citrate. There was one case of carcinoma of the urinary bladder, one case of carcinoma of the prostate, one case of carcinoma of the breast, and one case of malignant synovioma, all with metastases to bone.

#### MATERIAL AND METHODS

Radiogallium citrate was prepared as described previously<sup>1d</sup>; 1 ml. of gallium solution contained approximately 1 mc. of Ga<sup>72</sup> and 6 mg. of stable gallium, at pH 6.5, with an excess of citrate ions. Prior to administration, the patient received intravenously 500 mg. of calcium chloride in aqueous solution to prevent tetany due to the excess citrate which would immobilize the blood calcium. The radioactive solution was administered intravenously by means of a gravity-flow arrangement such that the flask tubes and needle were flushed with isotonic sodium chloride solution.

Patients thus treated were isolated but were not placed in shielded rooms. At no time was there more than one patient receiving Ga<sup>72</sup> in one ward. None of the patients required special nurses; consequently routine nursing procedures were adequate in all cases.

No special diets or drugs were necessary because of the gallium therapy. All the urine was collected at 24-hour intervals for 96 hours after injection, and the retention of gallium was estimated by radioassay performed on the urine specimens.

#### REPORT OF CASES

CASE 1.—A 61-year-old white man, a pharmacist, was admitted to this hospital April 18, 1950, with a diagnosis of transitional cell carcinoma of the bladder, which had been fulgurated on several previous occasions. In July he had x-ray therapy to the pelvis with good palliative effect. A Ga<sup>72</sup> tracer study done June 5 revealed areas of increased uptake over the eighth and ninth thoracic vertebrae, the second and third lumbar vertebrae, the pelvis bilaterally, and the proximal ends of both femurs. As a palliative measure, 269 mc. of Ga<sup>72</sup> was given from Aug. 20 through Jan. 8, 1951.

5. Dudley,<sup>1a</sup> Dudley, Imirie, and Istock.<sup>1c</sup>

6. King, Mason, Messinger, and Dudley.<sup>2c</sup> Mulry and Dudley.<sup>3</sup>

This patient, although negativistic toward any therapy, improved to the extent that an indwelling catheter required for several months was removed. Afterward he could void ad libitum. Two weeks after the therapeutic course was complete, he was able to be up and about in a wheel chair, although previously he had been bedridden.

X-ray examinations showed osteolytic lesions in the pelvis and lumbar spine throughout and after the course of Ga<sup>72</sup>. The patient died. The autopsy pathological diagnosis was transitional cell carcinoma of the bladder, with metastases to the prostate; seminal vesicles; regional lymph nodes; pleura and lungs bilaterally; preaortic lymph nodes; 4th, 5th, 8th, 9th and 11th thoracic vertebrae; 1st, 2d, and 3d lumbar vertebrae; 4th and 5th ribs on the left; right 5th rib; right and left ilium, and right femur.

CASE 2.— a 61-year-old white man, a metal worker, was first admitted to this hospital in November, 1947, at which time the diagnosis of Paget's disease and carcinoma of the prostate with metastases to the pelvis was made. He had previously undergone a prostatectomy for adenocarcinoma of the prostate. A bilateral orchiectomy was performed, and administration of diethylstilbestrol was started. Because of the progressive nature of the pain, he was given x-ray therapy to the pelvis, but without relief. A Ga<sup>72</sup> tracer study in March, 1950, revealed increased uptake over the metastatic lesions in the right pelvis. In April and May, he was treated with 26.5 mc., in July he received 9 mc., and from Oct. 16 through Dec. 18 he received 150 mc. of Ga<sup>72</sup>.

This patient, after the first and second single-dose therapies, reported marked relief of bone pain and was able to walk about more easily. After the intensive therapeutic course given late in 1950, the patient again claimed a reduction of bone pain. The patient's attitude tended toward euphoria, and this made it doubly difficult to evaluate his improvement.

X-ray examinations demonstrated a large dense osteoblastic mass in the right ilium. Two months after Ga<sup>72</sup> therapy, the center of the sclerotic lesion appeared less dense by x-ray. Whether or not this was a result of gallium therapy is debatable.

In February, 1951, the patient was admitted to the Medical Division of the Oak Ridge Institute of Nuclear Studies in Oak Ridge, Tenn., and died on . . . . . During this hospitalization period he received 441 mc. of Ga<sup>72</sup>. At autopsy there was a large, irregular, nodular, cystic lesion in the pelvis invading the ilium and pubic bones on the right and extending to the midline. The pubic bones on both sides were invaded with tumor. Histologically, the lesion was an adenocarcinoma of the prostate.

CASE 3.— a 29-year-old white woman, had a left radical mastectomy for adenocarcinoma of the breast in April, 1950. Because of rapid metastatic growth, a bilateral oophorectomy was performed in June; two courses of x-ray therapy were given in June, 1950, and January, 1951, and two courses of Ga<sup>72</sup> were administered in March and July of 1951. The first Ga<sup>72</sup> therapy was 317 mc. given over a period of 30 days. This was followed by subjective alleviation of bone pain. The second course was 190 mc. given over a period of 15 days. The first Ga<sup>72</sup> tracer study, in March, 1951, revealed no areas of increased uptake, but the second tracer study, in July, 1951, revealed areas of increased uptake over the upper and lower right ilium posteriorly. The patient was extremely cooperative and felt she received marked benefit from the first course of Ga<sup>72</sup> therapy. In the four-month interval between therapies, she showed x-ray evidence of bone healing of the inferior ramus of the right pubis, the right scapula, and possibly the first lumbar vertebra. Death occurred on . . . . . There was no local recurrence at the mastectomy site. Histologically, the tumor was a poorly differentiated adenocarcinoma with metastases to abdominal lymph nodes, diaphragm, liver, bone, pleura, and lungs.

CASE 4.— a 28-year-old Negro man, a teacher, was admitted to this hospital on June 11, 1951, where the diagnosis of synovial sarcoma of the right elbow with possible metastases to the fifth cervical vertebra was made. On June 21 a right mid-arm amputation was performed, with the removal of two axillary lymph nodes. Because of the onset of severe pain in the right shoulder and neck and the x-ray evidence of destruction of the body of the fifth cervical vertebra, the patient was given a course of Ga<sup>72</sup>, 73 mc. over a 14-day period (from Aug. 23 to Sept. 6). Because severe nausea developed, the Ga<sup>72</sup> therapy was discontinued. The pathological diagnosis was synovial sarcoma, right arm. The patient claimed no beneficial effect from Ga<sup>72</sup> therapy. Repeated x-ray examinations showed progressive osteolytic metastases throughout his hospital stay.

Details of Administration of Radioactive Gallium ( $Ga^{72}$ )

Case No.	Age, Yr.	Sex	Diagnosis *	Radioactive Gallium Administered (Mc.)	Stable Gallium Administered (Mc.)	Estimated Stable Gallium Retained (Mc. §)	Areas of Bone Destruction Shown by X-ray Examination	Laboratory Studies	
								Pretherapy	Post-Therapy
1	62	M	Transitional cell carcinoma of urinary bladder with bone metastases (A, B, C, X)	Single dose 8/29/50, 11.0 10/ 9/50, 22.3 11/ 3/50, 23.5 Therapeutic course of 6 weekly injections 12/4/50-1/8/51 Total 212 mc.	300	137	3d lumbar vertebra (1950), 11th and 12th thoracic vertebrae (8/17/50), L. ilium (12/2/50), upper ends of both femurs (2/20/51)	WBC 6700 (6/16/50)	WBC 3400 (1/11/51)
2	61	M	Carcinoma of the prostate with bone metastases (A, B, C, X)	Single dose 4/24/50, 14.0 5/29/50, 12.3 7/24/50, 9.2 10/10/50, 24.1 Therapeutic course of 6 weekly injections 11/13/50-12/18/50 Total 126 mc.	600	513	Lower 1/2 R. ilium, R. and L. pubis, R. and L. ischium, shaft of R. femur (3/20/50)	WBC 9400 (3/31/50) Acid phosphatase 17.6	WBC 8300 (12/16/50)
3	29	F	Carcinoma of breast with generalized bone metastases (A, B, O, X)	Therapeutic course of 8 semiweekly injections 3/12/51-4/16/51 Total 317 mc.	1,950	453	R. scapula, 1st lumbar vertebra, medial 1/2 of R. ilium, R. and L. acetabulum, inferior ramus of R. pubis and L. pubis (3/15/51)	WBC 6700 (3/8/51)	WBC 1625 (8/22/51) WBC 800 (8/24/51)
4	28	M	Malignant synovialoma with bone metastases (U, O, X)	Therapeutic course of 5 semiweekly injections 7/30/51-8/13/51 Total 190 mc.	880	628	5th cervical vertebra, upper end and shaft of R. humerus (8/8/51)	WBC 13,000 (6/13/51)	WBC 6800 (9/16/51)
				Therapeutic course of 4 weekly injections 8/23/51-9/13/51 Total 121 mc.	720	201		Alkaline phosphatase 11.6 (3/21/50)	

\* Diagnosis based on: (A) autopsy findings; (B) biopsy; (C) clinical impression; (X) x-ray findings.  
 † Effective half life of  $Ga^{72}$  in man is approximately 12 hr.  
 ‡ This is the nonradioactive gallium which accompanies the  $Ga^{72}$ .  
 § Estimated by study of the 0-48 hr. urinary excretion of  $Ga^{72}$ .

## COMMENT

The four patients reported on had incurable malignant conditions, the diagnoses of which were verified by surgical biopsy and autopsy. There were no possible therapeutic measures remaining for any of these patients.

From data which have been presented, three of the four patients given test therapy doses of  $Ga^{72}$  appeared clinically and/or subjectively to have received some benefit. Their lesions were so widespread that it would have been impossible to treat all bone metastases with palliative x-ray therapy. From previous experience, the relief of bone pain was in no case greater in these patients than in patients treated with x-rays. It is realized that subjective clinical findings cannot be depended upon to any great extent in the evaluation of a new drug.

In two patients there was continued progression of the bone lesions, as discerned by x-rays, throughout and after the course of therapy. One patient showed a decrease in density of a previous large sclerotic lesion of the ilium. This change in x-ray appearance has been known to occur in similar patients receiving no therapy. One patient had roentgenographic evidence of an increase in density of some lesions which might be attributed to an attempt at healing.

It was necessary to terminate  $Ga^{72}$  therapy in one case because of a marked leucopenia. In Case 3, the white blood cells dropped to 500, terminating the first course, and to about the same level during the second course.

Patient 1 had a dry, scaly erythematous rash about two weeks after the completion of his therapeutic course. Patient 3 complained of the same symptoms after a similar interval. Patients 1, 3, and 4 had severe nausea and vomiting after four or five injections (a total of about 500 mg. of stable gallium). Patient 4 had severe nausea and vomiting after the third and fourth injections, necessitating termination of the course.

Autopsy findings on the three patients who died substantiated the diagnosis but were not impressive in regard to beneficial results from  $Ga^{72}$  therapy. The results indicate that a toxic dose of carrier stable gallium is administered before it is possible to deliver an adequate dose of radiation to the bone lesions. This limiting factor of stable-gallium toxicity eliminated the use of  $Ga^{72}$  as a therapeutic agent under present methods of preparation and administration.

## SUMMARY

The clinical courses of therapeutic trials of radiogallium ( $Ga^{72}$ ) in four cases of incurable bone cancer have been presented.

The clinical results are indefinite so far as positive beneficial results are concerned.

Stable-gallium toxicity limits the amount of the radioactive gallium that can be administered. Consequently,  $Ga^{72}$  is not considered to be an effective therapeutic agent.

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