

⁶⁷Gallium in the Detection and Localization of Tumours*

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SUMMARY

The use of ⁶⁷Gallium citrate and gamma-imaging with a gamma camera as a diagnostic procedure for the detection and localization of malignant disease has been evaluated in 64 patients with malignant disease.

From the results obtained it can be concluded that ⁶⁷Gallium citrate can play an extremely useful diagnostic role as a tumour scanning agent. Best results are obtained in patients with sarcomata of any type and lymphomata. The procedure is less useful for the detection of carcinoma although diagnostically valuable information may be obtained with primary carcinoma of the maxillary antrum, breast and lung and in the case of metastatic carcinoma involving bone.

S. Afr. Med. J., 45, 1351 (1971).

Interest in the physiological significance of radioactive gallium and its compounds was first aroused when it was noted that this element is contained in fission products.¹

Subsequent studies on the metabolism of gallium indicated its usefulness in the study of bone metabolism.² Dudley and Maddox³ reported the accumulation of ⁷²Gallium citrate in bone with higher incorporation of radioactivity into areas of increased osteogenic activity. Dudley *et al.*⁴ investigating deposition of ⁷²Gallium in proliferating tissues, demonstrated significant uptake by bone tumours but no localization in certain soft tissue tumours.

A therapeutic trial of ⁷²Gallium citrate by Andrews *et al.*⁵ on 21 patients with bone tumours, showed a tendency for gallium to localize in areas of bone activity, whether osteoblastic or osteolytic, as well as high concentrations in highly cellular soft tissue tumours. Fairly high levels of radioactivity were also found in normal liver, spleen and bone marrow.

In 1965 Hayes *et al.*⁶ suggested the use of ⁶⁷Gallium citrate as a skeletal scanning agent, but found that objectionably high doses of stable carrier gallium needed to be given to obtain favourable bone : blood and bone : muscle concentration ratios, and to avoid an undesirable deposition in the liver and spleen. To overcome this difficulty Edwards and Hayes⁷ investigated the use of ⁶⁷Gallium since this isotope was available in the carrier-free state and had a more useful physical half-life. During the course of their studies they made the unexpected observation that radioactive gallium localized in the palpable cervical lymph nodes of a patient with Hodgkin's

disease, one of the first patients under study. In this paper they investigated 9 patients with soft tissue tumours and obtained positive scans in 7 cases, detecting not only known tumour deposits, but also tumours not known to be present.

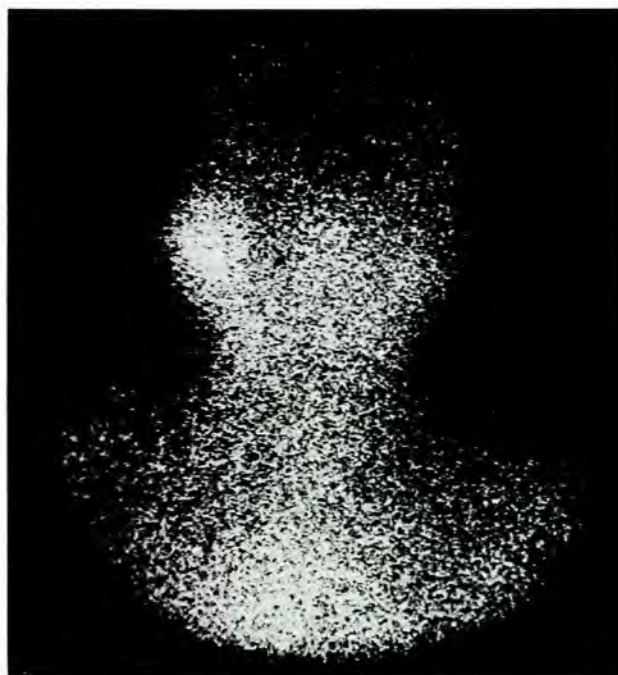
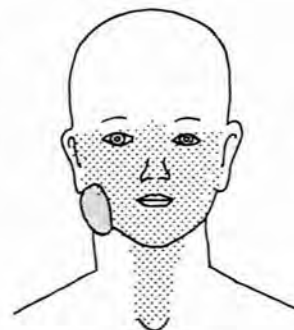


Fig. 1. Hodgkin's disease: Antero-posterior view head and upper thorax. Increased uptake can be seen in the upper cervical lymph nodes on the right. Note the normal uptake pattern of the face and mediastinum.



Subsequent clinical investigations into the use of ⁶⁷Gallium citrate as a tumour scanning agent have been reported by a number of workers. Higashi *et al.*^{8,9} obtained

*Date received: 8 October 1971.

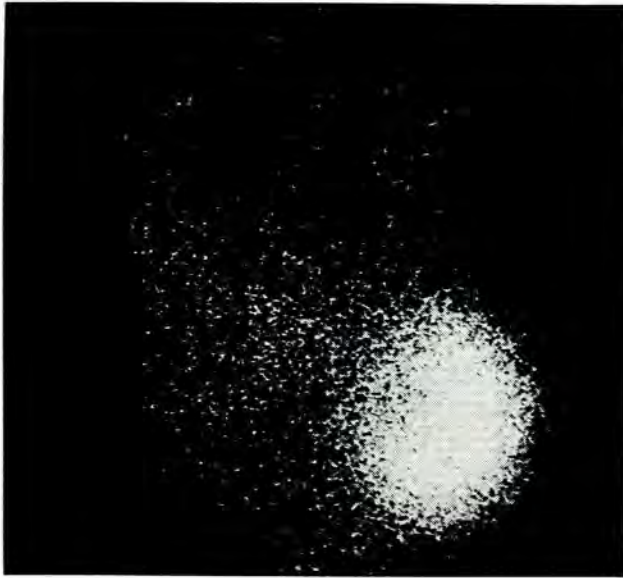


Fig. 2. Lymphosarcoma: Antero-posterior view head and neck. A marked area of uptake is present in the upper cervical lymph nodes on the left.

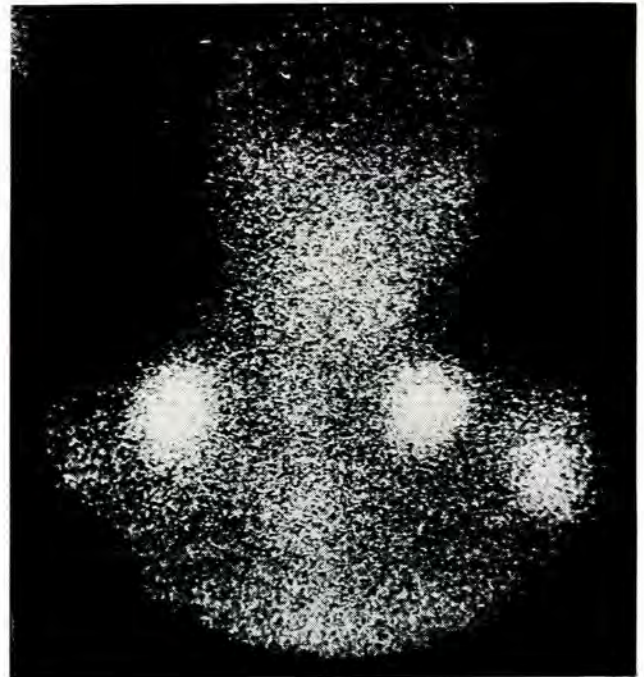
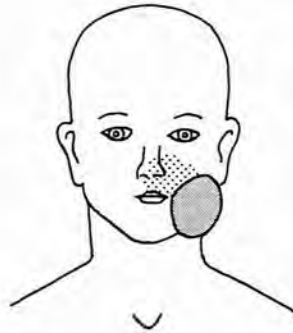


Fig. 3. Reticulum cell sarcoma: Antero-posterior view head, neck and upper thorax. Obviously abnormal uptake of ^{67}Ga is demonstrated in the apical lymph nodes of the left axilla and in both supra-clavicular regions.

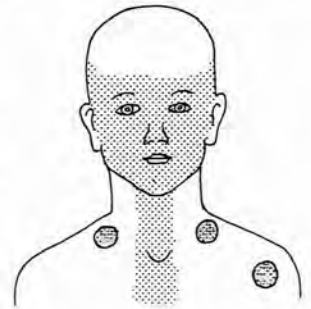


TABLE I. RESULTS OF SCANS PERFORMED IN PATIENTS WITH LYMPHOMA

	Present series	Higasi et al. 1969	Edwards and Hayes, 1970	Winchell et al. 1970	Lavender et al. 1971	Total
Hodgkin's disease						
Number of patients	2	1	11	4	1	19
Number of positive scans	1	1	6	4	1	13
Lymphosarcoma						
Number of patients	1	0	4	0	1	6
Number of positive scans	1	—	0	—	0	1
Giant follicular lymphoma						
Number of patients	1	0	2	1	0	4
Number of positive scans	1	—	2	1	—	4
Reticulum cell sarcoma						
Number of patients	3	0	6	0	0	9
Number of positive scans	2	—	6	—	—	8
Unspecified						
Number of patients	1					1
Number of positive scans	1					1
Total						
Number of patients	8	1	23	5	2	39
Number of positive scans	6	1	14	5	1	27

25 positive scans out of 37 patients studied with malignant tumours. Edwards and Hayes¹⁰ demonstrated 23 tumour sites sufficiently well to be considered clinically useful in 41 patients with a variety of neoplasms. Winchell *et al.*¹¹ studied 18 patients with various neoplastic disorders. Eleven of these subjects showed sufficient uptake of ⁶⁷Gallium to be useful in tumour localization. Lavender *et al.*¹² showed localized tumour uptake in 11 of 25 patients with malignant disease.

The mechanism causing increased gallium concentration in tumours is unknown. It has been suggested by Edwards and Hayes¹⁰ that it may be related to protein binding, although they point out that other nuclides with similar protein-binding properties to gallium, e.g. indium, do not accumulate in tumours in the same way. An alternative explanation by Winchell *et al.*¹¹ suggests a mechanism depending on pH changes favouring the formation of protein-metal complexes.

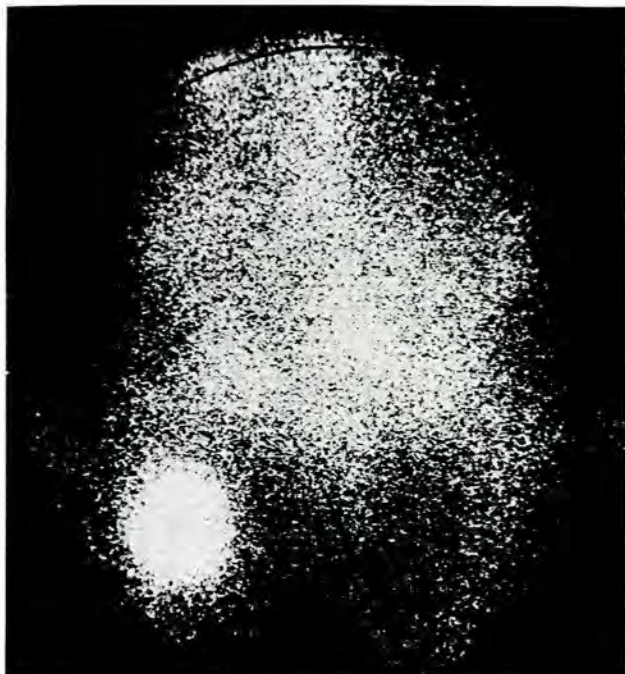
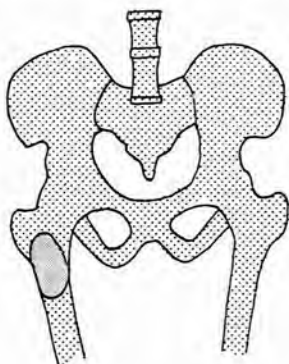


Fig. 4. Reticulum cell sarcoma: Antero-posterior view pelvis and proximal thighs. Increased uptake can be seen in a lesion of the right thigh. Note the normal uptake pattern of the female pelvis.



Edwards and Hayes¹⁰ observed that high uptake of gallium occurred in viable tumour tissue, necrotic or fibrotic tumours showing much less localization. This observation fits in with animal studies^{8,9,13} in which gallium was detected autoradiographically in the cytoplasm of viable tumour cells. In addition, accumulation was found to be greater in the peripheral zone than in the centre of the tumour, presumably due to vagaries of blood supply.

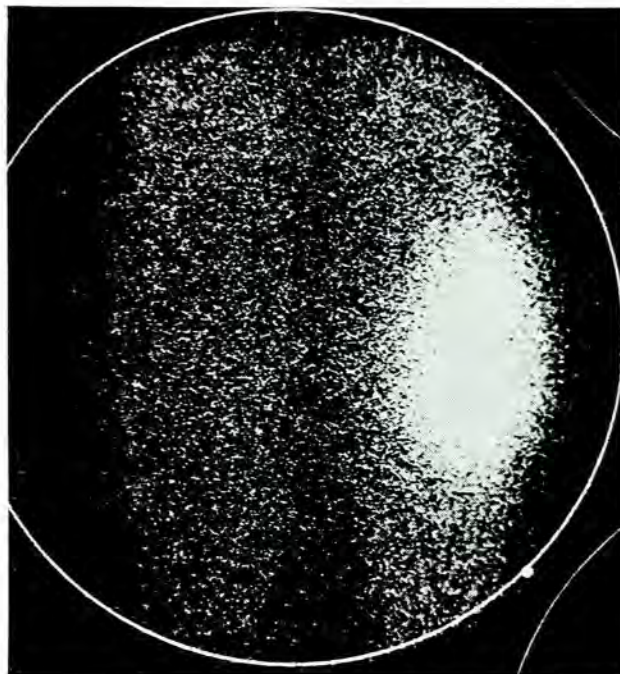
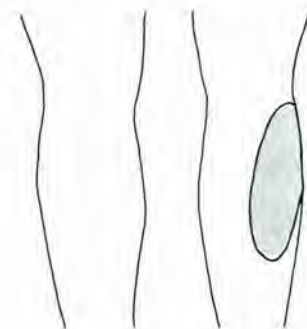


Fig. 5. Osteogenic sarcoma: Antero-posterior view of both calves. A marked area of uptake is shown by a lesion in the lateral aspect of the left calf.



In this article we report the results obtained in scanning patients with malignant disease using ⁶⁷Gallium citrate and we compare our results with those of other published series.

MATERIALS AND METHODS

⁶⁷Gallium citrate was obtained from the Nuclear Physics and Radioactivity Division at the National Physical Re-

search Laboratory of the South African Council for Scientific and Industrial Research.

It was produced by internal beam bombardment of a pure zinc target by 16 mev deuterons in a cyclotron. The target was left for 78 hours before processing to allow the short-lived ^{68}Ga isotope to decay. Chemical separation of ^{68}Ga from the zinc and copper of the target was achieved by cation exchange techniques. The carrier-free ^{68}Ga obtained was converted into a ^{68}Ga citrate solution containing 1.5% sodium citrate and 0.9% sodium chloride.



Fig. 6. Rhabdomyosarcoma: Postero-anterior view pelvis and upper thighs. A region of increased uptake is demonstrated in the right buttock.



^{68}Ga has a physical half-life of 78 hours and decays by electron capture. Gamma rays emitted range from an energy of 0.092 mev (42%) to 0.39 mev (7%).

Two millicuries of gallium citrate solution were injected intravenously, giving a whole body absorbed dose of 0.42 rads and an absorbed dose of ± 2 rads to the critical organs (liver, gonads, bone).¹⁴

Scans were performed 48 hours later on a Nuclear Chicago Pho-gamma III Gamma-Camera. The camera was set for optimal detection of the 0.092 mev gamma-rays of ^{68}Ga . A diverging collimator was used at a

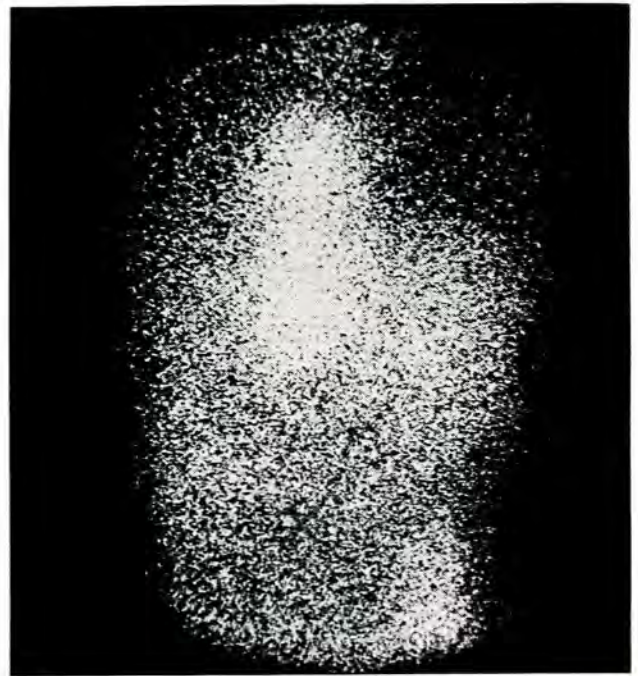


Fig. 7. Rhabdomyosarcoma. Postero-anterior view dorsal spine. Increased uptake can be seen over the spine in the region of the patient's backache.



TABLE II. RESULTS OF SCANS PERFORMED IN PATIENTS WITH SARCOMA (PRESENT SERIES)

	Number of patients	Number of positive scans
Osteogenic sarcoma	5	5
Osteoclastoma	1	1
Rhabdomyosarcoma	3	2 + ?
Chondrosarcoma	1	1
Fibrosarcoma	3	1
Liposarcoma	1	0
Undifferentiated	3	3
Total	18	14 + ?

patient-to-collimator distance adjusted to provide a field of view that would include the entire width of the supine body. As many fields were examined as were necessary to provide a view of the distribution of radioactivity in the whole body. If a suspicious area of increased radioactivity was noted in the antero-posterior view, additional views were taken with the patient so positioned as to aid final interpretation.

Patients were referred for this investigation by the Department of Radiotherapy. All tumours had previously been diagnosed by routine histological methods.

Lymphoma (Table I)

Eight patients with lymphomas were studied, positive scans were obtained in 6. In a patient with Hodgkin's disease good uptake was demonstrated in upper cervical lymph nodes (Fig. 1). A similar picture was seen in a patient with lymphosarcoma who had a large mass of glands in the neck (Fig. 2).

The patient with giant follicular lymphoma had been treated with radiotherapy in 1968 and presented 3 years later with a palpable lymph node in the groin that took up ⁶⁷Gallium.



Fig. 8. Carcinoma of the breast. Antero-posterior view chest and upper abdomen. A localized area of uptake is present in the right breast.

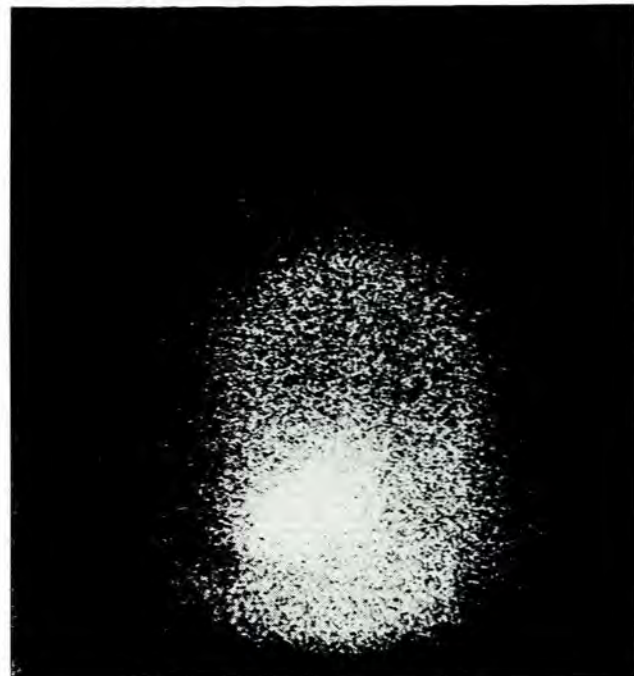
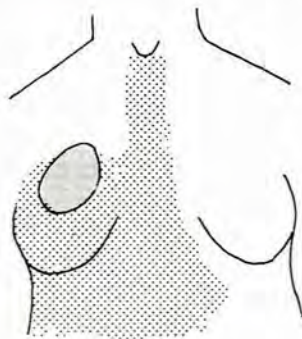
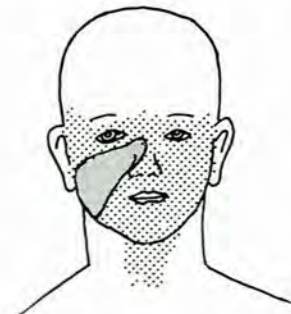


Fig. 9. Carcinoma of the maxillary antrum. Antero-posterior view of head. An area of increased uptake is present on the right side of the face in the area of the maxillary antrum.



RESULTS

Results of our findings in 64 patients with a variety of malignant diseases, compared with the findings in other published series are given in Tables I-V. Positive results were obtained in 29 of our cases.

Both patients with reticulum cell sarcoma who had positive scans had widespread disease. In one case, with a lesion in the right thigh, supraclavicular and axillary lymph nodes were shown to be involved (Figs. 3, 4), and in the other case, para-aortic lymph node uptake was demonstrated as was the primary site in the right groin.

A young female presenting with paraplegia was found on ^{67}Ga scanning to have a large paravertebral mass, the histology of which showed a lymphoma of uncertain type.

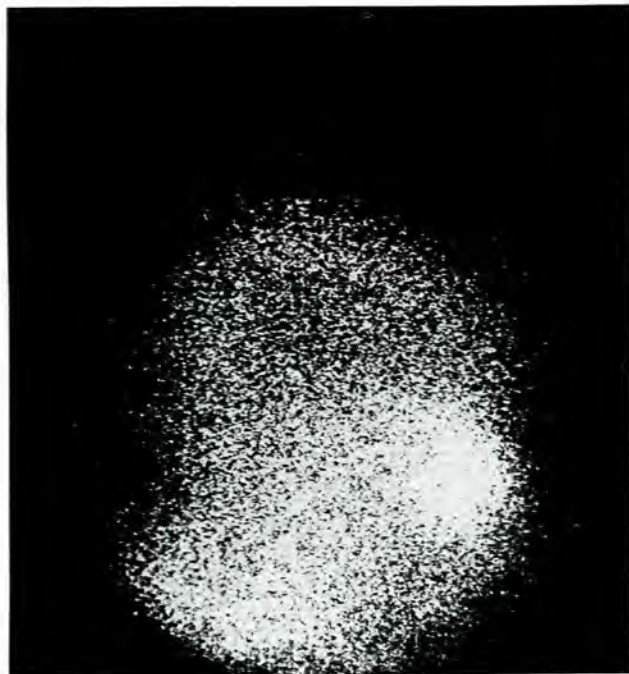
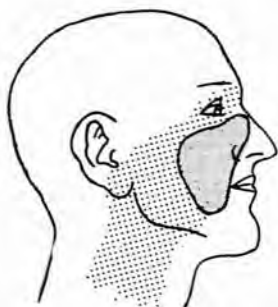


Fig. 10. Carcinoma of the maxillary antrum. Right lateral view of head. The area of abnormal radioactivity seen in Fig. 9 is seen in this view to be lying anteriorly.



Sarcoma (Table II)

Eighteen patients with sarcomata were scanned; 14 positive scans and one doubtful scan were obtained. Osteogenic sarcomata were present in 5 of the cases and all had positive scans (Fig. 5). A patient with rhabdomyosarcoma of the buttock, who complained constantly of backache was found to have uptake over the buttock lesion (Fig. 6) and also over the dorsal spine (Fig. 7). The latter lesion was later demonstrated radiographically.

Negative scans were obtained in 2 patients with fibrosarcoma and one with a retroperitoneal liposarcoma.

Adenocarcinoma (Table III)

Only 4 positive scans were obtained out of 13 patients studied with adenocarcinomas. One of these was obtained in a patient with a carcinoma of the breast (Fig. 8), and another in a patient with a pathological fracture of the right humerus that proved to be due to a metastatic deposit from an adenocarcinoma of uncertain origin.

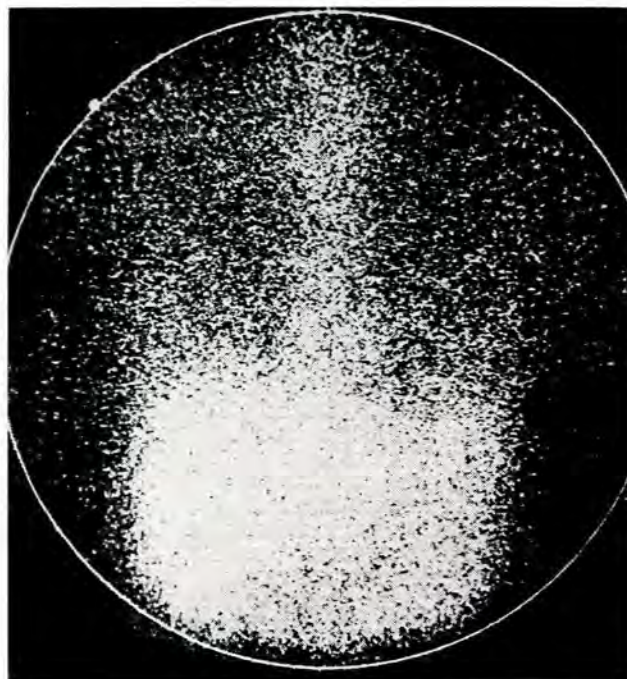
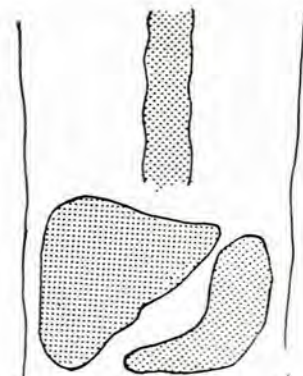


Fig. 11. Normal uptake pattern. Antero - posterior view of chest and upper abdomen. Uptake can be seen in the spine, liver and stomach.



Squamous Carcinoma (Table IV)

Of 10 patients studied only 3 showed positive scans. Extremely good uptake was shown by a carcinoma of the maxillary antrum (Figs. 9, 10). Positive scans were also

TABLE III. RESULTS OF SCANS PERFORMED IN PATIENTS WITH ADENOCARCINOMA

	Present series	Higasi et al. 1969	Edwards and Hayes, 1970	Winchell et al. 1970	Lavender et al. 1971	Total
Stomach						
Number of patients	3	2		2	2	9
Number of positive scans	0	?		1	1	2 + ?
Colon						
Number of patients	1				1	2
Number of positive scans	0				1	1
Breast						
Number of patients	1	10	2	1	15	29
Number of positive scans	1	7	1	0	6	15
Prostate						
Number of patients	1					1
Number of positive scans	1					1
Hypernephroma						
Number of patients	5					5
Number of positive scans	1					1
Thyroid						
Number of patients	1	1	2			4
Number of positive scans	0	1	0			1
Unspecified						
Number of patients	1		3			4
Number of positive scans	1		3			4
Total						
Number of patients	13	13	7	3	18	54
Number of positive scans	4	8 + ?	4	1	8	25 + ?

obtained in a patient with a Pancoast's tumour and in another with metastatic undifferentiated carcinoma.

An interesting finding was an area of increased uptake in the left side of the pelvis in a patient with carcinoma of the cervix that was found at operation to be due to a pelvic abscess.

Transitional Cell Carcinoma

A negative scan was obtained in one patient studied with a bladder carcinoma.

Other Malignancies (Table V)

Of 14 patients in this group, only 2 showed positive scans, both of whom had a malignant melanoma. In one case this involved the face and in the other metastatic involvement of lymph nodes in the neck. Both patients with malignant melanoma of the eye had negative scans as did the 4 patients with retinoblastoma.

DISCUSSION

Our findings in using ^{67}Ga citrate as a tumour localizing agent are similar to those of other groups.⁸⁻¹²

Of the lymphomas the best results were obtained with giant follicular lymphoma and reticulum cell sarcoma. Patients with Hodgkin's disease gave positive scans in approximately 70% of cases (13 out of 19 cases). Poor results were obtained with lymphosarcoma, our case, in fact, giving the only positive scan of the 6 thus far reported.

The best results in our series were obtained in patients with a wide variety of sarcomas. The only other patient with a sarcoma previously described was a patient with Ewing's sarcoma¹⁰ who had a positive scan. The success obtained in osteogenic sarcoma, osteoclastoma and chondrosarcoma is not surprising in view of the known tendency for gallium to accumulate in newly formed bone² and bone tumours.⁴

The carcinomas as a group gave the worst results with significant uptake occurring only in breast lesions ($\pm 50\%$ positive), lung lesions (75+% positive) and in undifferentiated adeno- or squamous carcinomas. Good results were obtained in carcinoma of the maxillary antrum. Poor results were obtained in lesions of the bowel and other intra-abdominal neoplasms.

Of the other malignancies studied it would appear that only malignant melanoma shows uptake of gallium with a 50% success rate.

In addition to localization in malignant tumours, ^{67}Ga citrate has also been found to accumulate in normal tissues, i.e. liver (Fig. 11), spleen, mediastinum (Fig. 1), bowel (Fig. 12), skeleton (especially female

TABLE IV. RESULTS OF SCANS PERFORMED IN PATIENTS WITH SQUAMOUS CARCINOMA

	Present series	Higasi et al. 1969	Edwards and Hayes 1970	Winchell et al. 1970	Lavender et al. 1971	Total
Cervix						
Number of patients	2					2
Number of positive scans	0				—	0
Tongue						
Number of patients	3					3
Number of positive scans	0				—	0
Maxillary antrum						
Number of patients	1	3				4
Number of positive scans	1	3			—	4
Retromalar space						
Number of patients	1					1
Number of positive scans	0				—	0
Lung						
Number of patients	1	14	4	1		20
Number of positive scans	1	11 + 2 ?	3	0	—	15 + 2 ?
Larynx						
Number of patients	1					1
Number of positive scans	0				—	0
Undifferentiated						
Number of patients	1		1			2
Number of positive scans	1		1		—	2
Total						
Number of patients	10	17	5	1		33
Number of positive scans	3	14 + 2 ?	4	0	—	21 + 2 ?

TABLE V. RESULTS OF SCANS PERFORMED IN PATIENTS WITH OTHER MALIGNANCIES

	Present series	Edwards and Hayes, 1970	Winchell et al. 1970	Lavender et al. 1971	Total
Wilms' tumour					
Number of patients	2				2
Number of positive scans	0				0
Multiple myeloma					
Number of patients	1	3			4
Number of positive scans	0	0			0
Retinoblastoma					
Number of patients	4				4
Number of positive scans	0				0
Seminoma					
Number of patients	1		1		2
Number of positive scans	0		0		0
Histiocytosis X					
Number of patients	1				1
Number of positive scans	0				0
Mesothelioma					
Number of patients	1				1
Number of positive scans	0				0
Malignant melanoma					
Number of patients	4			2	6
Number of positive scans	2			1	3
Total					
Number of patients	14	3	1	2	20
Number of positive scans	2	0	0	1	3

pelvis—Fig. 4), breast tissue in a patient with gynaecomastia¹¹ and in the normal breast.⁹

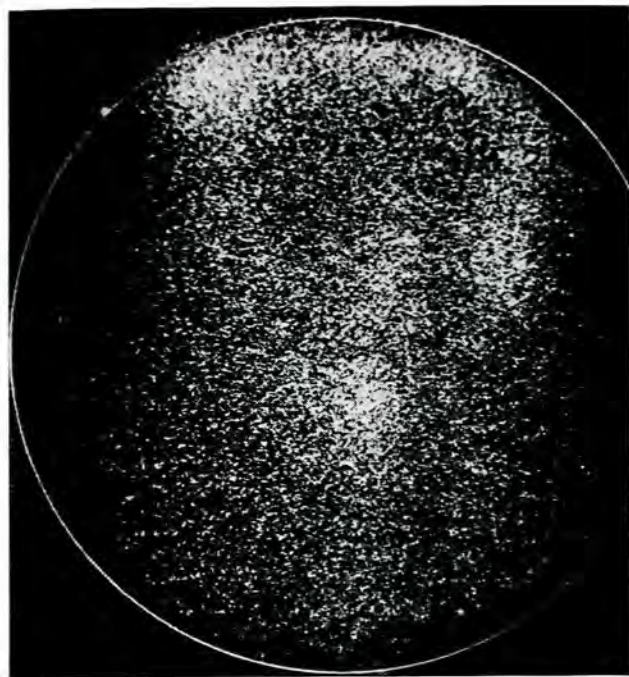
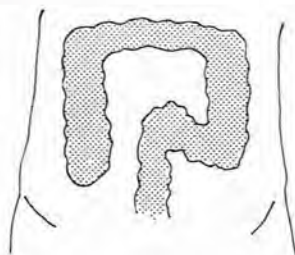


Fig. 12. Normal uptake pattern. Antero - posterior view of abdomen. Uptake can be seen in the ascending, transverse, descending and sigmoid colon and rectum.



Benign tumours do not appear to accumulate ⁶⁷Gallium. Higasi *et al.*⁸ studied uptake in a small number of benign tumours and obtained only one positive scan, in a case of

cystic mastitis, in which they attributed the uptake to associated inflammation.

Inflammatory conditions have, however, been found to give rise to positive scans. Higasi *et al.*⁸ obtained a positive scan in one case of active tuberculosis, and doubtful scans in 5 other cases. Tuberculoma (2 cases), non-active tuberculosis (2 cases), pneumonia (2 cases), and pleurisy (1 case) all gave negative scans. Positive scans were also obtained in 3 cases with inflammation of the submaxillary salivary gland. Hisada and Hiraki¹⁰ reported a case of pneumonia with a strongly positive scan. Lavender *et al.*¹² obtained positive scans in one patient with a lung abscess and in another with breast abscesses. In our series we obtained a positive scan in a patient with a pelvic abscess.

The authors acknowledge with thanks the help of Drs J. Steyn and W. Rautenbach of the Nuclear Physics and Radioactivity division at the National Physical Research Laboratory of the South African Council for Scientific and Industrial Research, K. Baker Associates for loan of the gamma camera, Dr R. Sealy and the Staff of the Department of Radiotherapy for their full and valuable co-operation and Dr J. G. Burger, Medical Superintendent, Groote Schuur Hospital, for permission to publish.

REFERENCES

1. Plutonium Project (1946): *J. Amer. Chem. Soc.*, **68**, 2411.
2. Dudley, H. C., Maddox, G. E. and La Rue, H. C. (1949): *J. Pharmacol. Exper. Ther.*, **96**, 135.
3. Dudley, H. C. and Maddox, G. E. (1949): *Ibid.*, **96**, 224.
4. Dudley, H. C., Imrie, G. W. and Istock, J. T. (1950): *Radiology*, **55**, 571.
5. Andrews, G. A., Root, S. W. and Kerman, H. D. (1953): *Ibid.*, **61**, 570.
6. Hayes, R. L., Carlton, J. E. and Byrd, B. L. (1965): *J. Nucl. Med.*, **6**, 605.
7. Edwards, C. L. and Hayes, R. L. (1969): *Ibid.*, **10**, 103.
8. Higasi, T., Ikemoto, S., Nakayama, Y., Hisada, T., Suzuki, S., Tanada, I., Kato, H., Murata, A., Sugiyama, M. and Osita, S. (1969): *Japanese Journal of Nuclear Medicine*, **6**, 217.
9. Higasi, T., Hisada, T., Nakayama, Y., Kinoshita, Y., Kawai, K., Suzuki, S., Kato, H., Murata, A., Sugiyama, M., Kawaguchi, R. and Nakamura, I. (1970): *Radio Isotopes*, **19**, 17.
10. Edwards, C. L. and Hayes, R. L. (1970): *J. Amer. Med. Assoc.*, **212**, 1182.
11. Winchell, H. S., Sanchez, P. D., Watanabe, C. K., Hollander, L., Anger, H. O., McRae, J., Edwards, C. L. and Hayes, R. L. (1970): *J. Nucl. Med.*, **11**, 459.
12. Lavender, J. P., Lowe, J., Barber, J. R., Burn, J. I. and Chaudhri, M. A. (1971): *Brit. J. Radiol.*, **44**, 361.
13. Hayes, R. L., Nelson, B., Swartzendruber, D. C., Carlton, J. E. and Byrd, B. L. (1970): *Science*, **167**, 289.
14. Popham, M. G., Taylor, D. M. and Trott, N. G. (1970): *Brit. J. Radiol.*, **43**, 807.
15. Hisada, K. and Hiraki, T. (1970): *Igaku no Ayumi*, **72**, 590.