FROM RADIUMHEMMET (DIRECTOR: PROF. J. EINHORN), STOCKHOLM, SWEDEN.

# INTRAARTERIAL DISTRIBUTION OF COLLOIDAL BISMUTH COMPOUNDS INJECTED IN MAN

by

G. LUNDELL

A considerable amount of the $^{206}Bi$ acetate in saline injected intravenously or intraarterially is absorbed during its first capillary passage (EINHORN et coll. 1964). The distribution of four bismuth compounds has been examined, special attention being paid to the possibility of their accumulation in tumours situated distally to the site of their arterial injection. Colloidal compounds of bismuth have been proposed for systemic and local use in the treatment (KAHN 1930, VAN DER WERFF 1958, 1965, MATTHEWS 1962) and diagnosis (VAN DER WERFF 1966, GERHARD et coll. 1964) of malignant tumours. It has also been suggested that the accumulation of colloidal solutions with certain properties may have therapeutic implications for the administration of compounds of short-lived isotopes in perfusion therapy (BROWNELL et coll. 1960).

The four compounds of $^{206}Bi$ used in the investigation were the acetate in isotonic saline and in 5 per cent glucose, the nitrate in dilute $HNO_3$ and the sulphide in human albumin. The activity ranged from 0.5 to 1 mCi/ml.

*Material.* The case material and the compounds used are presented in the Table.

Submitted for publication 14 December 1971.

**Table**

*The patients examined after injection of various $^{206}Bi$ compounds into an iliac artery*

| Case No. | Sex | Age | Disease | Compound used | Activity injected ($\mu$Ci) |
|---|---|---|---|---|---|
| 1 | M | 15 | Osteogenic sarcoma in lower part of left femur | Bi acetate in saline | 750 |
| 2 | M | 17 | Ewing's sarcoma in left femur | Bi acetate in saline | 660 |
| 3 | M | 15 | Osteogenic sarcoma in middle of left tibia | Bi acetate in saline | 600 |
| 4 | M | 67 | Carcinoma of bladder; no skeletal metastases | Bi acetate in glucose | 650 |
| 5 | F | 68 | Mammary carcinoma with metastases in femur | Bi nitrate in dilute $HNO_3$ | 900 |
| 6 | M | 62 | Carcinoma of bladder; no metastases | Bi nitrate in dilute $HNO_3$ | 800 |
| 7 | M | 70 | Carcinoma of mouth and lower lip; no metastases | Bi sulphide in 2 % human albumin | 700 |
| 8 | F | 57 | Myeloma in left leg | Bi sulphide in 2 % human albumin | 500 |

*Methods.* The bismuth compounds were injected into the left or right external iliac artery by the percutaneous technique; the injection was made on the affected side when a tumour was present.

The examination was carried out as whole-body scanning and by profile diagram measurement. The LKB whole-body scintigraph (JONSSON et coll. 1957) was used at a detector speed of 600 mm/min, a line space of 24 mm and a scale factor of 20 or above. In view of the high energy of the gamma radiation from $^{206}Bi$, a focussing collimator was incorporated and beneath which a specially designed extra lead shield was mounted; this produced a shielding of at least 10 cm of lead in all directions except at the collimator opening. The detector consisted of a thallium-activated sodium iodide crystal, 3 inches (7.6 cm) thick and 3 inches (7.6 cm) in diameter; the scanner was equipped with a single-channel pulse-height analyzer. The measurement was begun from the head downwards within 1.5 hours of the injection of the radioactive compound and repeated at different intervals up to 4 days.

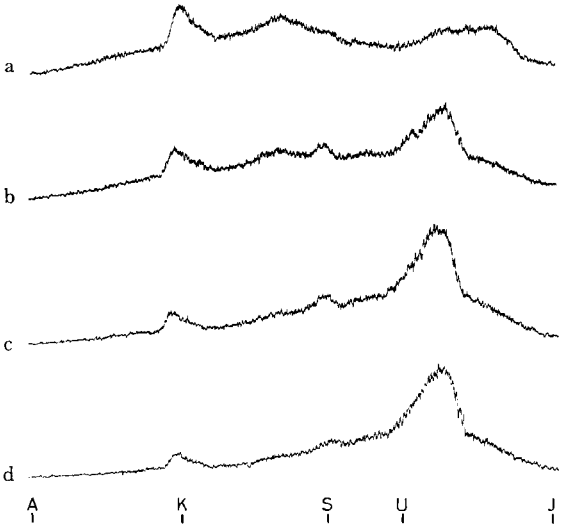


Fig. 1. Case 1. Osteogenic sarcoma of the left femur. Profile scanning. Measurements at 20 min (a), 9.5 (b), 30.5 (c) and 52.5 (d) h after the injection of $^{206}$Bi acetate in saline. Levels indicated: A — ankle, K — knee, S — symphysis, U — umbilicus, J — jugulum.

## Results

*$^{206}$Bi acetate in saline.* Cases 1, 2 and 3. High counting rates were recorded initially in order of diminishing activity: the tumour area, adjacent areas distal to the injection site, thorax and the abdomen (Figs 1 a, 2 a). The accumulation in the tumour area diminished rapidly in the first few hours after the injection, and a transfer of activity towards the abdominal region occurred (Figs 1 b, c, 2 b, c).

*$^{206}$Bi acetate in glucose.* Case 4. Carcinoma of bladder with no signs of leg involvement. Two hours after the injection an accumulation of the isotope, decreasing peripherally, appeared in the leg on the side of the injection; this was also evident in the thorax and upper abdominal region (Fig. 3 a). Only an extremely small amount of activity remained in the leg at 19 hours (Fig. 3 b).

*$^{206}$Bi nitrate.* Cases 5 and 6. The distribution and time sequence were similar to those for the acetate in glucose.

*$^{206}$Bi sulphide.* Cases 7 and 8. Ninety minutes after the injection no accumulation of the compound was evident in the leg on the side of the injection either in the myeloma case (Case 8) or in the one with no leg involvement (Case 7). Most of the activity was in the upper abdominal region corresponding to the area of the liver (Figs 4, 5).

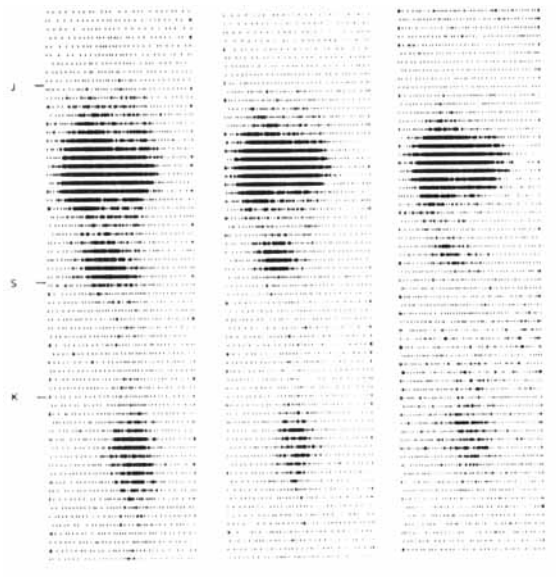


Fig. 2. Case 3. Osteogenic sarcoma of the left tibia. Scintigraphy. Scanning started 2.5 (a), 8 (b) and 25.5 (c) h after the injection of $^{206}$Bi acetate in saline. The isotope accumulation in the middle part of the left tibia was greatest at the examination 2.5 h after the injection, following which there was a rapid decrease. Levels indicated: K — knee, S — symphysis, J — jugulum.

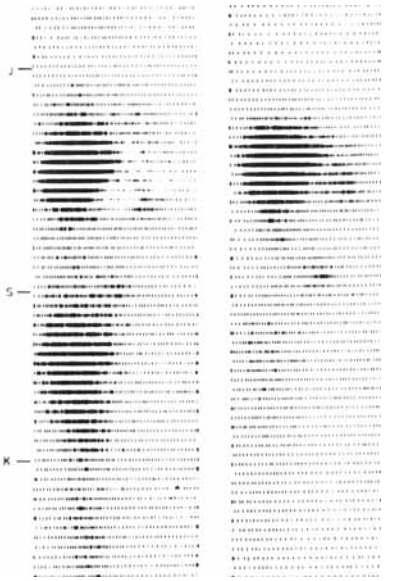


Fig. 3. Case 4. Scintigraphy. Scanning started 2 (a) and 19 (b) h after the injection of $^{206}$Bi acetate in glucose revealed an initial accumulation in the right femur and to a lesser extent in the right tibia. No signs of tumour involvement of leg.

## Discussion

During the first passage through the vascular system much of the bismuth acetate in saline or in glucose and the bismuth nitrate injected were probably filtered off by the capillary system and remained in the tissues in the region. In view of the nature of the changes in the leg, the series is too small and lacking in homogeneity to permit any definitive conclusions regarding the differences between the four compounds of bismuth. The most stable of them, the sulphide, would however seem to be transported more rapidly to the liver and spleen. The reason for this is probably that the three less stable compounds soon form larger aggregates in the blood, most of them then being removed from the circulation by filtration in the capillary system. The redistribution of the colloid towards the abdominal region is probably due to a gradual breakdown of the aggregates that are then accumulated in the reticuloendothelial system and possibly also excreted by the kidneys.

Fig. 4

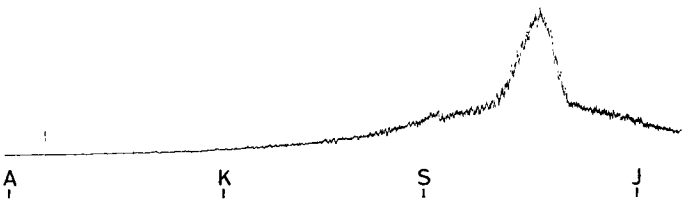


Fig. 5

Fig. 4. Case 7. Scanning started 1 h and 40 min after the injection of $^{206}$Bi sulphide in 2 per cent human albumin. No tumour of the leg.

Fig. 5. Case 7. Profile scanning. Measurement 1.5 h after the injection.

As all the compounds investigated remained for only a short time even in highly vascular tumours (Cases 1, 2, 3) they seem unsuitable for intraarterial therapy; the redistribution to other organs occurs too soon.

## Conclusions

Various $^{206}$Bi compounds were injected into the external iliac artery in 5 patients with skeletal tumours in one leg and in 3 patients without signs of tumour involvement of the legs. A fair amount of the acetate and nitrate preparations persisted in the leg distally to the site of injection. It is suggested that this was probably due to filtration during the first capillary passage. The cases with a tumour situated distal to the artery into which the acetate or nitrate was injected was however redistributed rapidly to the liver, spleen and lungs. The accumulation in the tumours was of too short a duration to provide favourable conditions for selective radiation therapy by the intraarterial injection of an isotope compound with a half-life period of $^{206}$Bi.

## SUMMARY

The requirements for the use of various compounds of $^{206}$Bi for selective radiation therapy by intraarterial injection were examined in 8 cases in which the isotope was injected into an iliac artery. An accumulation in the tumour area was obtained with some of the compounds. Redistribution occurred so rapidly, however, that the technique must be considered unsuitable for intraarterial isotope therapy.

## ZUSAMMENFASSUNG

Die Forderungen für die Anwendung verschiedener Verbindungen von $^{206}$Bi für die selektive Radiotherapie durch intraarterielle Injektion wurden in 8 Fällen untersucht, in denen das Isotop in die A. iliaca injiziert wurde. Mit einigen der Verbindungen wurde eine Akkumulation im Tumorgebiet erreicht. Die Redistribution war jedoch so rasch, dass die Technik für die intraarterielle Isotoptherapie als ungeeignet betrachtet werden muss.

## RÉSUMÉ

L'auteur a examiné sur 8 cas où l'isotope a été injecté dans une artère iliaque les conditions requises pour l'emploi de différents composés de $^{206}$Bi pour la radiothérapie sélective par injection intra-artérielle. Certains des composés se sont accumulés dans la région tumorale. La redistribution était cependant si rapide que cette technique ne convient probablement pas pour le traitement intra-artériel par les isotopes.

## REFERENCES

BROWNELL G. L., ELLETT W. H., OJEMANN R. G. and SWEET W. H.: The use of shortlived isotopes in the perfusion therapy of isolated organs. Strahlentherapie (1960) Sonderband 45, p. 126.

EINHORN J., ENGSTEDT L., FRANZÉN S. and LUNDELL G.: Distribution of colloidal Bismuth intravenously and intraarterially administered in man. Acta radiol. Ther. Phys. Biol. 2 (1964), 443.

GERHARD H., GABRIEL E., MUNDINGER G. und WALDBAUR H.: Neuere Untersuchungen über die Tumoranreicherung radioaktiver Schwermetallisotope ($^{203}$Hg, $^{206}$Bi und $^{64}$Cu). *In:* Radionuklide in der klinischen und experimentellen Onkologie, p. 229. F. K. Schattauer-Verlag, Stuttgart 1964.

GRAUL E. H. und HUNDESHAGEN H.: Tierexperimentelle Untersuchungen mit $^{206}$Bi-Kohlesuspension. Atompraxis 4 (1958), 324.

JONSON L., LARSSON L.-G. and RAGNHULT I.: A scanning apparatus for the localization of gamma emitting isotopes in vivo. Acta radiol. 47 (1957), 217.

KAHN H.: Die Ablagerung von aktivem Wismut in malignen Tumoren. Strahlentherapie 37 (1930), 751.

— Behandlung maligner Geschwülste mit radioaktivem Wismut (Radium E). Dtsch. med Wschr. 50 (1930), 2131.

MATTHEWS C. M. E.: Irradiation of lymph nodes. Clin. Sci. 22 (1962), 209.

PASSALACQUA F.: Verteilungsprüfungen von verschiedenen Radio-Wismut-Verbindungen $^{206}$Bi bei normalen und splenektomierten Ratten. Strahlentherapie 102 (1957), 606.

SOLLMAN T. and SEIFTER J.: The toxicity of bismuth salts by intravenous injection. J. Pharmacol. exp. Ther. 72 (1941), 39.

VAN DER WERFF J. TH.: Radiowismut in der Therapie. Atompraxis 4 (1958), 319.

— Radioactive bismuth $^{206}$Bi. Experimental studies and clinical applications. Acta radiol. (1965) Suppl. No. 243.

— Gamma encephalography with radioactive bismuth 206. Acta radiol. Ther. Phys. Biol. 4 (1966), 403.