6. *Code of practice on radiation safety in government hospitals.* Hong Kong: Hong Kong Medical and Health Department; 1988.
7. *World Health Organization handbook for reporting results of cancer treatment.* Geneva: World Health Organization; 1979.
8. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer* 1985;15:918–928.
9. Ingold JA, Reed GB, Kaplan HS, Bagshaw MA. Radiation hepatitis. *Am J Roentgenol* 1965;93:200–208.
10. Robertson JM, Lawrence TS, Dworzanin LM, et al. Treatment of primary hepatobiliary cancers with conformal radiation therapy and regional chemotherapy. *J Clin Oncol* 1993;11:1286–1293.
11. Order SE, Stillwagon GB, Klein JL, et al. Iodine-131-antiferritin, a new treatment modality in hepatoma: a Radiation Therapy Oncology Group study. *J Clin Oncol* 1985;3:1573–1582.
12. Order S, Pajak T, Leibel S, et al. A randomized prospective trial comparing full dose chemotherapy to ^{131}I-antiferritin: an RTOG study. *Int J Radiat Oncol Biol Phys* 1991;20:953–963.
13. Fox RA, Klemp PF, Egan G, Mina LL, Burton MA, Gray BN. Dose distribution following selective internal radiation therapy. *Int J Radiat Oncol Biol Phys* 1991;21:463–467.
14. Yoo HS, Lee JT, Kim KW, et al. Nodular hepatocellular carcinoma. Treatment with subsegmental intraarterial injection of iodine-131-labeled iodized oil. *Cancer* 1991;68:1878–1884.
15. Raoul JI, Bretagne JF, Caucanas JP, et al. Internal radiation therapy for hepatocellular carcinoma. Results of a French multicenter phase II trial of transarterial injection of iodine-131-labeled Lipiodol. *Cancer* 1992;69:346–352.
16. Shiu W, Dewar G, Leung N, et al. Hepatocellular carcinoma in Hong Kong: a clinical study on 340 cases. *Oncology* 1990;47:241–245.

EDITORIAL

Iodine-131-Lipiodol for Hepatocellular Carcinoma: The Benefits of Targeting

Primary hepatocellular carcinoma is one of the most common malignant tumors in the world. It is responsible for an estimated 1 million deaths annually (*1*). HCC is especially prevalent in Southeast Asia, Japan (where it ranks second only to stomach cancer as a cause of death) and sub-Saharan Africa (*2*). The incidence in some Chinese provinces exceeds 75 cases per 100,000 people per year (*3*), and in males in Mozambique, the incidence is as high as 113 cases per 100,000 people per year (*4*). The disease is endemic in some African populations: a study of autopsies performed on the East African Bantu revealed evidence of HCC in four of every five people (*5*). By contrast, there is a low incidence in Northern Europe (around 2 per 100,000 people annually), but it is increasing in the United Kingdom (*6*), Scandinavia (*7*) and the United States, where the incidence in some states multiplied threefold in the past 20 yr (*8*). I remember discussing HCC with a research fellow from Nigeria, and asking him whether they had much HCC. He replied "three of my fellow medical students have died of HCC—is that a lot?"

HCC nearly always arises on the basis of underlying cirrhosis. For many years it has been appreciated that this is especially the case where the cirrhosis followed infection with the hepatitis B virus. The prevalence of HCC in the third world is associated with chronic hepatitis B infection, often transmitted from mother to child. We now appreciate that the majority of other cases arise following infection with hepatitis C.

The tumor often presents late, which, with underlying cirrhosis, makes surgery difficult or impossible in many patients. The median survival of patients with unresectable HCC may be as low as 3.5–7.5 wk.

In this issue, Leung et al. (*9*) report on HCC treatment using Lipiodol as a means of delivering targeted ^{131}I to the tumor. Lipiodol (iodized oil fluid injection (BP); ethiodized oil injection (USP)) is a lipid derived from the iodination of poppy seed oil and contains 475 mg of iodine per ml (38% by weight). It has been used for many years as a radiological contrast medium (its first recorded use as an angiographic medium was in 1923, when Sicard and Forestier injected the iodized oil into the antecubital vein of a patient to observe flow through the heart and pulmonary arteries (*10*)). In 1979, Nakakuma et al. injected Lipiodol into the hepatic end of the ligated hepatic artery and demonstrated its selective retention in foci of hepatocellular carcinoma (*11*). Lipiodol-enhanced arteriography is particularly effective in demonstrating the small "daughter" nodules often found in association with the main tumor mass of HCC (*12–14*). In technologically advanced countries this has become a part of the standard investigation of patients with suspected HCC, with CT being performed about 10 days after intra-arterial Lipiodol, when HCC may be clearly seen (*15*).

In 1985, Ohishi et al. (*16*) reported the results of treating HCC with Lipiodol carrying a chemotherapeutic agent (mitomycin C or Adriamycin) administered via the hepatic artery, and followed by embolization of the artery with Gelfoam particles. They reported reductions in tumor size, decreases in alpha-feto-protein (AFP) levels and survival rates of 89% at 6 mo and 69% at 1 yr in a population apparently selected only on the basis of being inoperable by virtue of cirrhosis or tumor size. In 1986, Kobayashi et al. (*17*) reported a further series of 41 patients treated in this way, but also on 7 patients treated with Lipiodol in which some of the iodine had been replaced by ^{131}I using exchange labeling. The Lipiodol was administered into one of the two main hepatic arteries, and all the patients showed a decrease in AFP levels and a reduction in tumor size. In one patient who died of liver failure 2 mo after therapy,

Received May 3, 1994; accepted May 5, 1994.
For correspondence or reprints contact: Andrew J. Hilson, Royal Free Hospital, Dept. of Nuclear Medicine, Pond St., London NW3 2QG England.

there was necrosis of the tumor. Takayasu et al. (*2*) showed that the effect was specific to chemo-embolization, not Lipiodol alone or gelfoam embolization.

Also in 1986, Park et al. (*18*) confirmed the feasibility of using ^{131}I-Lipiodol, and in 1987 they reported on a series of 47 patients (*19*). They were only able to follow-up about half of their patients for 3 mo, but nevertheless the results were encouraging. In 1988, Cho et al. (*20*) reported that 8 out of 14 of their patients were alive 12 mo after therapy. In 1988, Park et al. (*21*) and Nakajo et al. (*22*) both published data on a limited series of patients showing that the biodistribution and dosimetry were satisfactory for routine use.

Bourguet et al. (*23*) subsequently showed that not only was there selective uptake of ^{131}I by HCC, but also that tumor washout was slower than from normal liver. They reported encouraging results in 15 patients, in two of whom the results were sufficiently good to allow for transplantation (*24*). This was followed by a French multicentre Phase II study of 50 patients. This study showed a substantial benefit from therapy, which correlated with the degree of localization. At 120 wk, 50% of patients with the whole tumor localized by Lipiodol were alive, and 35% of those with over half the tumor volume localized survived (*25*).

The paper by Leung et al. in this issue adds to our experience by demonstrating that it is possible to give the therapy in divided doses through an implanted catheter (not as straightforward as it sounds, since Lipiodol dissolves some plastics). This extends the effective treatment half-life of Lipiodol.

Alternative methods of therapy using Lipiodol as a carrier for chemotherapy are being developed. For instance, in 1989 Nakamura (*26*) reported excellent survival rates (54% at 1 yr) in patients treated with Lipiodol-doxorubicin. The majority of these were in Okuda stage I (early) disease, and it is not clear how many were inoperable. More recently, Ngan et al., also from Hong Kong, showed good survival in patients treated with intra-arterial Lipiodol-Cisplatin, with a 1-yr survival rate of 53% (*27*).

Therefore, the question arises which is the better therapy: Lipiodol plus radioactivity or Lipiodol plus a chemotherapeutic agent. In our unit, we have now treated 95 patients with at least 6-mo follow-up, (69 with Lipiodol-Epirubicin and 26 with ^{131}I-Lipiodol). This includes those in a randomized trial comparing a fixed dose of 1 GBq (25 mCi) of ^{131}I-Lipiodol with Lipiodol-Epirubicin. Preliminary analysis of the results suggests that the two approaches give similar results, with survival depending mainly on the Okuda staging. However, patients receiving ^{131}I-Lipiodol have fewer side-effects. Bourguet et al. (personal communication) carried out a similar controlled trial comparing higher activities of ^{131}I-Lipiodol with Lipiodol-Cisplatin rather than Epirubicin, and again found similar survival rates with the two strategies, although the overall survival is better with the more potent therapies. Bourquet et al. have also shown in a randomized control trial that this approach could be used in patients with a blocked portal vein in whom no other interventional treatment is available. The survival rates at 3, 6 and 9 mo in the treated population were 71%, 57% and 57%, compared with 18%, 0% and 0%, respectively (*28*).

What are the lessons from ^{131}I-Lipiodol therapy in HCC? Leung et al. have underlined objective measures of response to ^{131}I-Lipiodol therapy. They have shown the feasibility of a fractionated approach when large tumors demand a high dose. Lipiodol therapy, whether with ^{131}I or with a chemotherapeutic agent, works. The data provide a salutary reminder that selective targeting may be achieved by physical as well as molecular methods. We spend much time devising clever molecular methods of getting our agents to their effector sites. Administering them by a radiological catheter can be fast, effective and safe. We owe it to our patients to demonstrate not only that these therapies are effective, but also that they are at least as effective as alternative methods, or less toxic, or both.

J.R. Novell
A.J.W. Hilson
Royal Free Hospital
and School of Medicine
London, England

REFERENCES

1. London W. Primary hepatocellular carcinoma—etiology, pathogenesis and prevention. *Hum Pathol* 1981;12:1085–1097.
2. Takayasu K, Shima Y, Muramatsu Y, et al. Hepatocellular carcinoma: treatment with intraarterial iodized oil with and without chemotherapeutic agents. *Radiology* 1987:162;345–351.
3. Bosch FX, Munoz N. Hepatocellular carcinoma in the world: epidemiologic questions. In: Tabor E, Di Biscaglie AM, Purcell RH, eds. *Etiology, pathology and treatment of hepatocellular carcinoma in North America (Advances in applied biotechnology series*, volume 13). Houston: Portfolio; 1991:35–54.
4. Muir C. *Cancer incidence in five continents* volume 5. Lyon, France: International Agency for Research in Cancer; 1987.
5. Berman C. Primary cancer of the liver in the Bantu races of South Africa. *S. African J Med Sci* 1940;5:54–72.
6. Burnett RA, Patrick RS, Spilg WCS, et al. Hepatocellular carcinoma and hepatic cirrhosis in the west of Scotland: a 25-year necropsy review. *J Clin Pathol* 1978;31:108–110.
7. Munoz N, Bosch FX. Epidemiology of hepatocellular carcinoma. In: Okuda K, Ishak KG, eds. *Neoplasms of the liver.* Tokyo: Springer-Verlag; 1987:3–19.
8. Peters RL, Afroudakis AP, Tatler D. The changing incidence of association of hepatitis B with hepatocellular carcinoma in California. *Am J Clin Pathol* 1977;68:1–7.
9. Leung WT, Lau WY, Ho S, et al. Selective internal radiation therapy with intra-arterial iodine-131-Lipidiol in inoperable hepatocellular carcinoma. *J Nucl Med* 1994;35:1313–1318.
10. Sicard JA, Forestier G. Injections intravascularies d'huile iodee sous control radiologique. *C R Soc Biol (Paris)* 1923;88:1200.
11. Nakakuma K, Tashiro S, Uemura K, et al. An attempt for increasing effects of hepatic artery ligation for advanced hepatoma [English abstract]. *Jap-Deutsche Med Berichte* 1979;24: 675–682.
12. Puech JL, Rousseau H, Portalez D, et al. Hepatic artery lipiodolization and computed tomographic diagnosis of malignant liver tumours. Experience with thirty-three cases [English abstract]. *Ann Radiol* 1987;30:193–201.
13. Hayashi N, Yamamoto K, Tamaki N, et al. Metastatic nodules of hepatocellular carcinoma: detection with angiography, CT and US. *Radiology* 1987;165:61–63.
14. Novell JR, Dusheiko G, Hilson AJW, et al. Lipiodol computed tomography for small hepatocellular carcinomas. *Lancet* 1991;337:333–334.
15. Yumoto Y, Jinno K, Tokuyama K, et al. Hepatocellular carcinoma detected by iodized oil. *Radiology* 1985;154:19–24.

16. Ohishi H, Uchida H, Ohue H, et al. Hepatocellular carcinoma detected by iodized oil: use of anticancer agents. *Radiology* 1985;154:25–29.
17. Kobayashi H, Hidaka H, Kajiya Y, et al. Treatment of hepatocellular carcinoma by transarterial injection of anticancer agents in iodized oil suspension or of radioactive iodized oil solution. *Acta Radiol Diagnost* 1986;27:139–147.
18. Park CH, Suh JH, Yoo HS, et al. Evaluation of intrahepatic ^{131}I-ethiodol on a patient with hepatocellular carcinoma: therapeutic feasibility study. *Clin Nucl Med* 1986;11:514–517.
19. Park CH, Suh JH, Yoo HS, et al. Treatment of hepatocellular carcinoma (HCC) with radiolabelled Lipiodol: a preliminary study. *Nucl Med Commun* 1987;8:1075–1087.
20. Cho YD, Yum HY, Park BC and Park YH. Intra-arterial ^{131}I-Lipiodol treatment in the management of primary carcinoma of the liver. *Proceedings of Chinese Academy of Med Sci and the Peking Union Medical College*, 1988; 3(suppl 1):49.
21. Madsen MT, Park CH, Thakur ML. Dosimetry of iodine-131 ethiodol in the treatment of hepatoma. *J Nucl Med* 1988;29:1038–1044.
22. Nakajo M, Kobayashi H, Shimabukuro K, et al. Biodistribution and in vivo kinetics of iodine-131-Lipiodol infused via the hepatic artery of patients with hepatic cancer. *J Nucl Med* 1988; 29:1066–1077.
23. Raoul J-L, Bourguet P, Bretagne J-F, et al. Hepatic artery injection of I-131-labeled lipiodol. Part I: biodistribution studies results in patients with hepatocellular carcinoma and liver metastases. *Radiology* 1988;168:542–545.
24. Bretagne J-F, Raoul J-L, Bourguet P, et al. Hepatic artery injection of ^{131}I-labeled lipiodol. Part II: preliminary results of therapeutic use in patients with hepatocellular carcinoma and liver metastases. *Radiology* 1988;168:547–550.
25. Victor G, Bourguet P, Therain F, et al. Treatment of hepatocellular carcinoma (HCC) by transarterial injection of ^{131}I-iodized oil. Results of a French multicenter Phase II trial [Abstract]. *Eur J Nucl Med* 1990;16:193.
26. Nakamura H, Hashimoto T, Oi H, Sawada S. Transcatheter oily chemoembolization of hepatocellular carcinoma. *Radiology* 1989;170:783–786.
27. Ngan H, Lai CL, Lai ECS, Yuen WK, Tso WK. Treatment of inoperable hepatocellular carcinoma by transcatheter arterial chemoembolization using an emulsion of cisplatin in iodized oil and gelfoam. *Clin Radiol* 1993;47:315–320.
28. Bourguet P, Raoul J-L, Guyader D, et al. Randomized control trial for hepatocellular carcinoma with portal vein thrombosis: intra-arterial injection of ^{131}I-labeled iodized oil versus medical support [Abstract]. *Eur J Nucl Med* 1992; 19:608.