Virchows Arch. A Path. Anat. and Histol. 382, 63–71 (1979)

Virchows Archiv A

Double Tumours of the Liver Following Intravenous Thorotrast Injection

Patho-Anatomical Report on Two Cases

Kurt Wegener and Sabine Leipolz-Angermüller

Pathological Institute of the Municipial Hospital of Ludwigshafen/Rh. (Director: Prof. Dr. K. Wegener), Bremserstr. 79, D-6700 Ludwigshafen/Rh., Federal Republic of Germany

Summary. Observations on the contrast between the livers of two patients who underwent an arteriogram with thorotrast in 1941 have been made. The first case produced a cholangicellular carcinoma (CCC) in addition to atypical proliferations of sinusoidal lining cells. The second case produced a very rare tumour combination of a CCC with a haemangioendothelial sarcoma (Haem-Sa). The problem of double tumours of the liver following thorotrast injection is discussed in the light of these cases. In addition the discussion includes various opinions on Kupffer cells.

Key words: Arteriogram following thorotrast injection – Proliferation of sinusoidal lining cells – Haemangioendothelial sarcoma – Cholangiocellular carcinoma

Introduction

Major studies on thorotrast carried out in different countries (da Silva Horta, 1965; Faber, 1967; van Kaick et al., 1973) report an above average incidence of Haem-Sa, hepatocellular carcinoma (HCC) and CCC some decades after intravenous injection of the radioactive contrast medium. The increase in liver tumours is explained by the radiation and foreign body effects of almost complete storage of thorotrast for many decades in the RHS (liver, spleen, lymph nodes, bone marrow). These liver tumours appear very rarely in patients who have not had thorotrast administered – Edmondson (1958) found 81 HCC, 86 CCC, and only one single Haem-Sa in 52,000 autopsies carried out during the period 1918–1954. It is remarkable that until now only one case of double tumour of the liver in the form of a Haem-Sa (mesodermal origin) and a CCC (entodermal origin) has been observed following thorotrast administration to humans (Barousch, 1969). Guimaraes et al. (1955) reported double tumours of the liver in animals, a malignant endothelioma combined with a hepatoma, and a Haem-Sa combined with a hepatoma.

0340-1227/79/0382/0063/$01.80

Spontaneous double tumours of the liver (HCC and CCC) in humans were first recorded by Wells in 1903, later by Allan and Lisa in 1949, and by Edmondson in 1958. In 1972 Vilsfeldt et al., in a thorotrast study, reported a liver tumour which consisted partly of a HCC and partly of a CCC. In these latter cases the tumours originate from the same germ layer (endoderm). Doubts have been expressed by some authors (Altmann, 1976) about their histogenic origin.

We report a fully developed form of double tumour of the liver derived from the components of two germ layers following thorotrast injection, and a possible preliminary stage in this process.

Case Reports

Case 1 (Path. Inst. Mannheim, autopsy: 996/76)[1]: 63-year-old male patient K.H.; in 1941 injury by gunshot wound in the right groin; arteriogram with thorotrast. Diagnosis: traumatic vessel rupture, arteriovenous aneurysm. Since 1954 he had had recurrent pains in the right upper part of the abdomen. In 1976 the patient died of heart failure.

[1] We would like to thank Prof. Dr. U. Bleyl, director of the Path. Institut des Klinikums Mannheim der Universität Heidelberg and Prosector Dr. H. Peter, director of the Path. Institut des Stadtkrankenhauses Bamberg for the pathological material

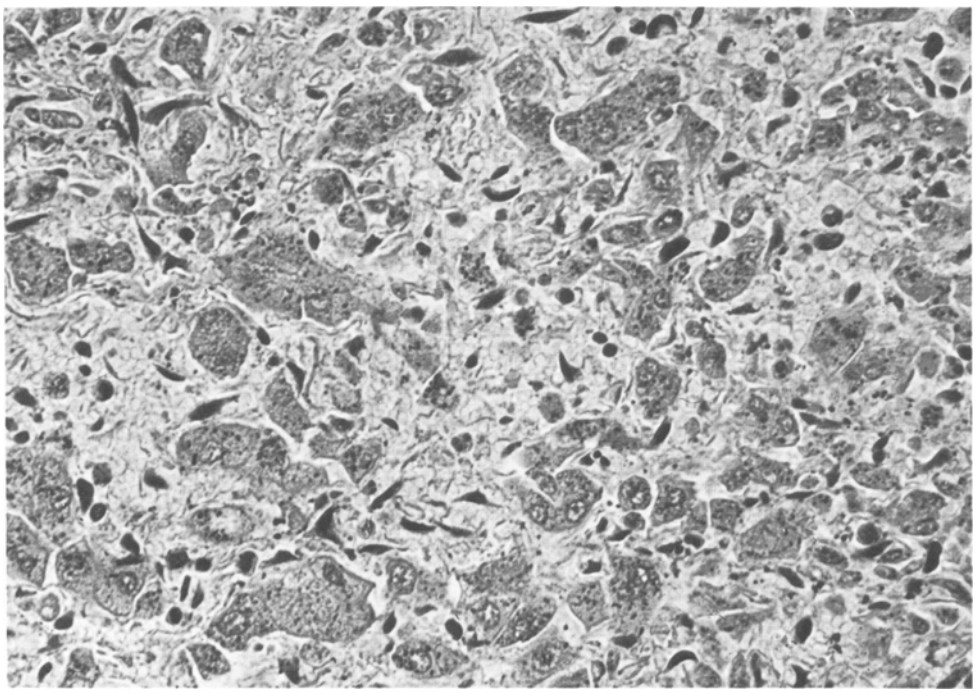

Fig 1. Prominent sinusoidal lining cells. Dilatation of the sinusoids. (Haematoxylin-Eosin; 200×

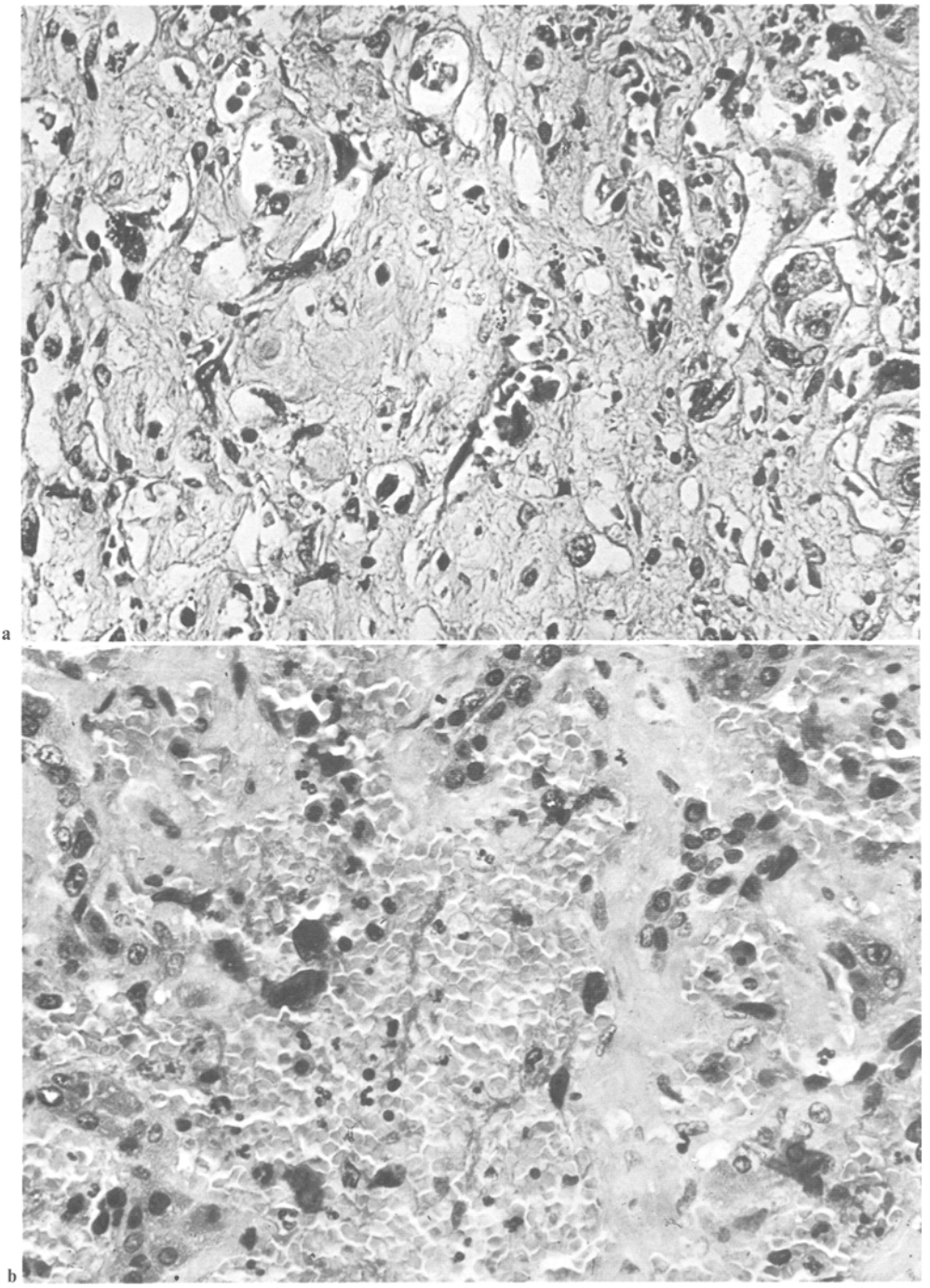

Fig. 2a and b. Atypical and bizarrely formed sinusoidal lining cells. (Haematoxylin-Eosin; 350×)

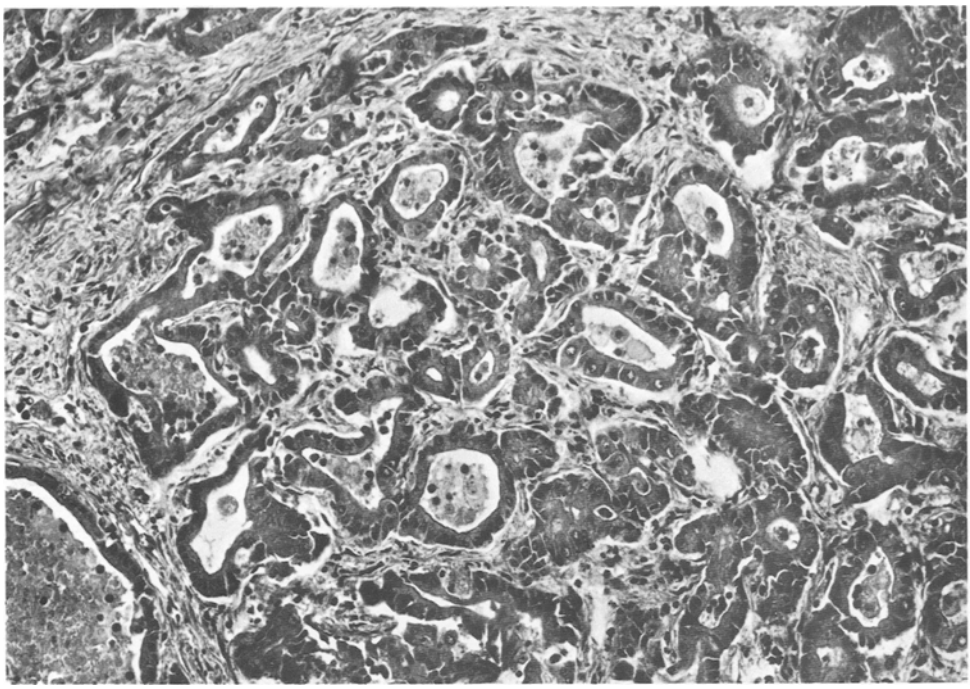

Fig. 3. Infiltrative growing CCC (Cholangiocellular Carcinoma). (Haematoxylin-Eosin; 140 ×)

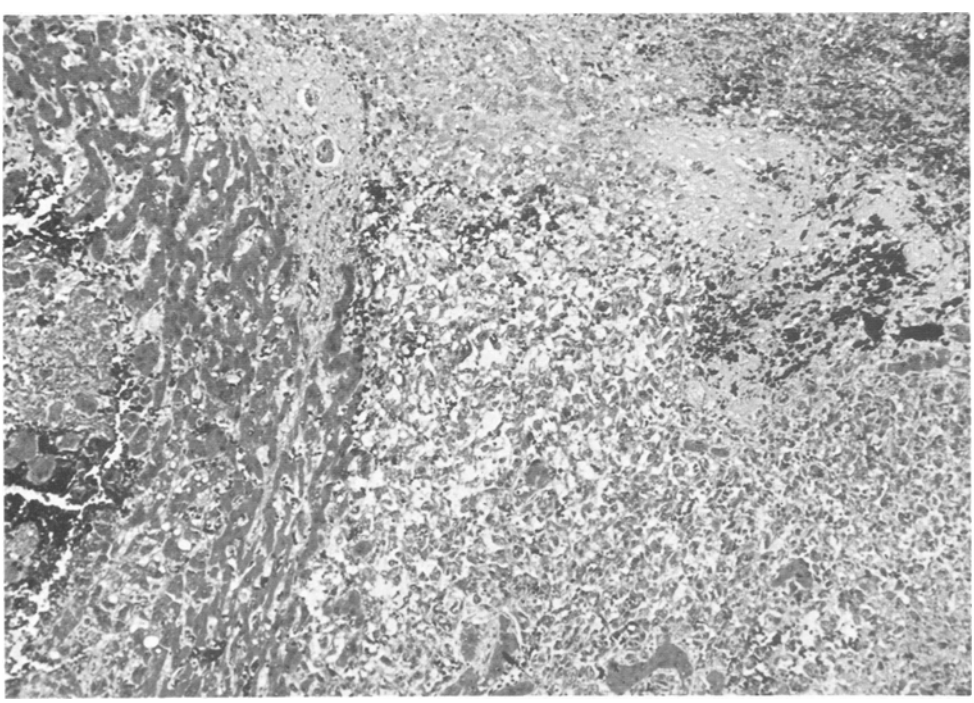

Fig. 4. Infiltrating and destructive growth of Haemangioendothelio-Sarcoma. On the left: Liver cells and dilatated sinusoids; on the upper right thorotrast particles. (Haematoxylin-Eosin; 100 ×)

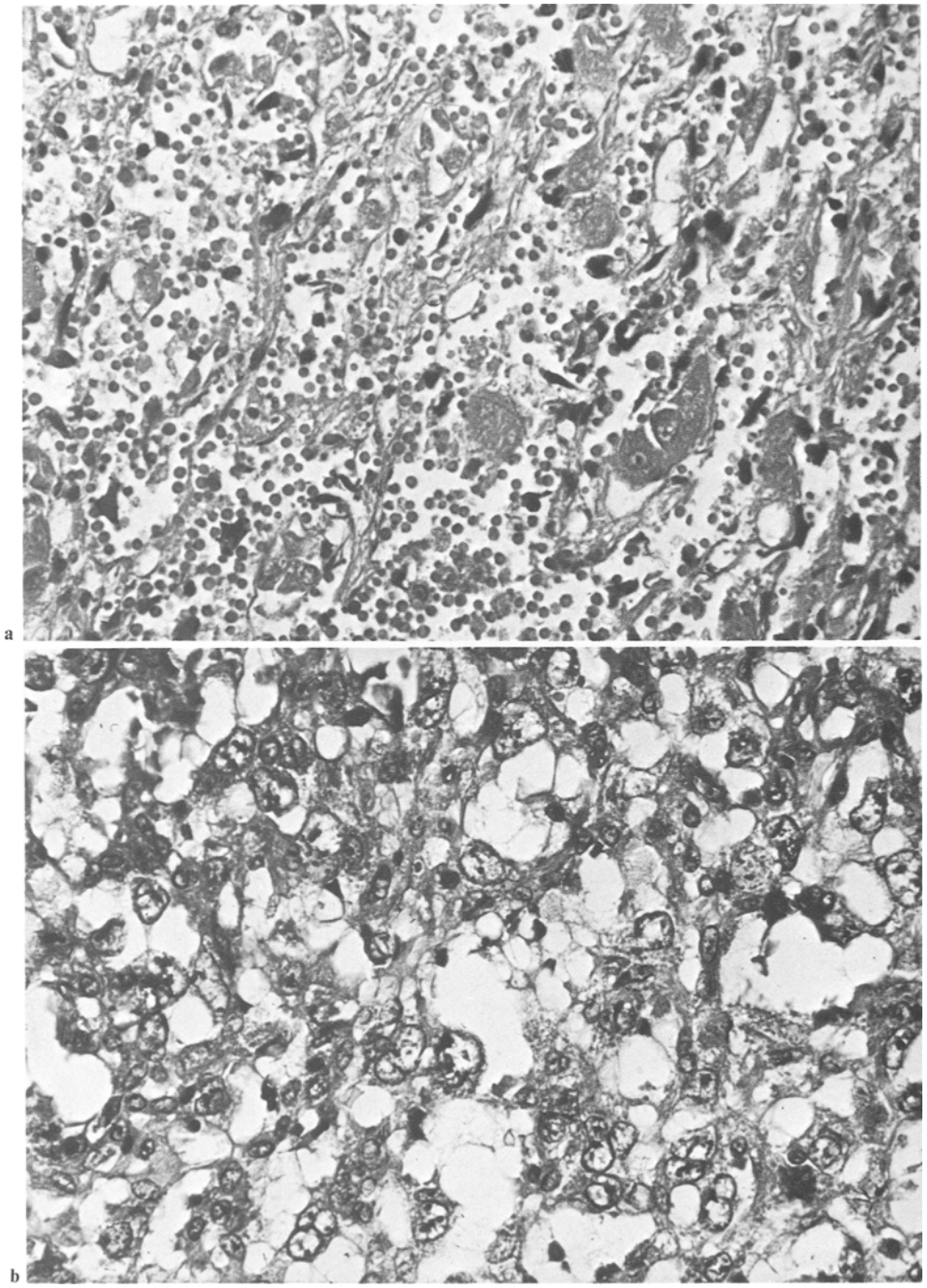

Fig. 5a and b. Two different areas of Haemangioendothelio-Sarcoma with reticular spreading of tumour cells. Fig. 5b makes it understandable why this type of tumour is called "reticulo-sarcoma" (Becker and Büsscher, 1961). (Haematoxylin-Eosin; 400×)

Macroscopic Diagnosis. Minor evidence of jaundice of the whole body. Hepatomegaly. Liver surface divided by very closely approximated bloody areas of different sizes. Areas of necrosis up to 5 × 4 cm in size are found in both lobes of the liver. Severe pressure atrophy of the remaining parenchyma. Fibrosis of the spleen. Several sharply defined, rough, white, cherry-sized areas in all lung segments and in the left adrenal gland.

Histological Diagnosis. Infiltrating and destructive growth of CCC of the liver with complete destruction of the lobules (Fig. 3). Prominent activity of the sinusoidal lining cells (Fig. 1) with the formation of atypical and bizarrely formed cells (Fig. 2a and b) Atrophic lobules. Dilatation of the sinusoids to form irregular cyst-like haemorrhagic spaces. Extensive necrosis. Patchy fibrosis of the portal areas with varying thorotrast deposits. Metastases of CCC in both lungs and in the left adrenal gland.

Case 2 (Path. Inst. Bamberg, biopsy: 13092/75)[2]: 47-year-old female patient H.A.; epileptic attacks at the age of 12; in 1941 arteriogram with thorotrast. Diagnosis: angioma of the right cerebral hemisphere. Surgical removal of the tumour. Damaged liver since 1970. Acute pain in the right upper abdomen November 3, 1975. Generalized jaundice. Acute shock november 8, 1975. Decrease of haemoglobin; intra-abdominal bleeding of unknown origin; erosive haemorrhagic gastritis; death of the patient in hypovolaemic shock November 26, 1975.

Macroscopic Diagnosis. Generalized jaundice. Haemorrhagic ascites (about 3,500 ml). Confluent, sponge-like, haemorrhagic nodes with grey-to-yellow coloured centres (15 × 8 cm) as well as several, smaller, haemorrhagic nodes in the left lobe of the liver (max. ∅ 1 cm). Two ruptured nodes with subcapsular haemorrhages and blood clots in the right lobe of the liver. Moderate fibrosis of the capsule and of the liver parenchyma. Severe fibrosis with distinct shrinkage of the spleen. Severe fibrosis of the para-aortal lymph nodes. Moderate oesophageal varices in the cardiac region. Bleeding into the parenchymatous organs caused by shock.

Histologic Diagnosis. Infiltrating growth of CCC (Fig. 3). Haem-Sa (Fig. 4) with reticular spreading of tumour cells (Fig. 5a and b). Ectasia of the sinusoids of the liver between the haemorrhagic nodes. Activation of the Kupffer cells. Central lobular necrosis. Fatty degeneration of the liver cells. Fibrosis of the portal areas with thorotrast deposits.

Discussion

HCC and CCC of the liver are clearly defined tumours. In contrast malignant angiosarcomas of the liver are less well defined with disputes on the grounds of nomenclature, histogenesis and morphology. Of the numerous types so far discovered, four have been classified by Becker and Büsscher (1961):

type I: diffuse haemangioendotheliomatosis
type II: reticulosarcoma angioplasticum (v. Albertini)
type III: reticulosarcoma haemorrhagicum (Roth)
type IV: reticulosarcoma solidum

A survey of the literature reveals 86 angiomas of the liver classified according to the above four types. In our first case we find changes resembling diffuse haemangioendotheliomatosis in type I. Grampa et al. (1967) have used the same description in an animal experiment with thorotrast. The morphology of our second case corresponds to type III (Figs. 4, 5a, 5b). Of six thorotrast cases registered by Becker et al. (1961), four are of type III. Both Grampa et al. (1958) and da Silva Horta (1965) have concluded that Haem-Sa is "thorotrast-specific". However, this point of view is not acceptable as Roth in 1957, found

[2] Footnote see p. 64

several Haem-Sa in vineyard workers exposed to arsenical insecticides who had accumulated significant amounts in their liver over long periods. In addition Popper et al. (1975), Thomas (1975), Gedigk et al. (1975), Berk et al. (1976), Gokel et al. (1976), and Popper et al. (1977) have described Haem-Sa found in workers in the polyvinylchloride industry. The initial stages of Haem-Sa, indicated by proliferation of the sinusoidal lining cells as in our first case, have been described by these authors, and by Tanikawa et al. (1977). From these observations it cannot be excluded that in addition to the effect of radioactivity, a foreign body effect may also share responsibility for tumour development following thorotrast application. To clarify this question an investigation has been initiated by the working group on foreign body reaction of thorotrast (Leipolz-Angermüller, 1976). From light-microscopic investigations it was established that the Kupffer cells, an important part of the RES, stored a great deal of thorotrast. It was thus understandable that Haem-Sa were diagnosed as Kupffer cell sarcomas. As a result of α-radiation, the stored contrast medium could well have caused malignant change in Kupffer cells. The fact that neither tumour cells of the Haem-Sa (case 2) nor the proliferating cells (case 1) store thorotrast (Higgins, 1970), presents some difficulties in establishing their origin.

There are two conflicting opinions about Kupffer cells. These are:

1. Kupffer cells and endothelial cells are merely two different kinds of one cell having different functions.

2. Kupffer cells are independent endocytes lying in the capillary space and connected to the sinusoidal wall by pseudopodia.

Becker et al. (1961) and Niculescu et al. (1967) present an extended review of the available literature.

Using modern techniques the question of the nature of Kupffer cells has been solved. Endothelial cells and Kupffer cells may be differentiated by SEM (Motta, 1975), TEM (Wisse, 1977), and by histochemistry (Strauss, 1964). There is no transitional stage between the two types of cell (Frenzel et al., 1974). Kupffer cells are macrophages (Carr, 1977) which originate from the transformation of blood monocytes (Carr, 1970).

At present three points require clarification:

1. Are the cells of Haem-Sa and its initial stage derived from only one of the cell types, and, if so, from which one?

2. Are certain Haem-Sa and their initial stages derived from Kupffer cells, while others are derived from endothelial cells?

3. Is the ability to carry out phagocytosis lost in malignant Kupffer cells?

A further problem concerns the question of why the combination of the two tumours, as described by us, appears so seldom in thorotrast patients. The following proposals are offered as possible explanations; firstly that the combination is more frequent than is apparent, but there are cases which have not been subjected to post-mortem examination or have not been reported, secondly that patients with Haem-Sa or carcinoma generally die before a second tumour becomes established or finally that for the development of a tumour, α-radiation is not the only factor, at least one other factor, e.g. "foreign body effect" is also important. The probability of both factors interacting in two histogenetically different cell types is very low.

It will only be possible to answer these questions by histochemistry and electron microscopy. This type of research will be very difficult with material derived from thorotrast patients as, only very rarely, is sufficient frozen or fixed tissue at one's disposal. Animal experiments therefore remain the most likely method of solving these problems. It is for this reason that we have carried out our studies in the hope that it will further the work of the foreign body effect of thorotrast group.

References

Allen, R.A., Lisa, J.R.: Combined liver cell and bile duct carcinoma. Am. J. Path. **25**, 647–655 (1949)

Altmann, H.W.: Bemerkungen zur Bewertung und Bezeichnung menschlicher Lebertumoren. Verh. Dtsch. Ges. Path. **60**, 408 (1976)

Barousch, R.: Thorotrastschäden. Eine Übersicht und Bericht über drei Fälle. Wiener Med. Wschr. **41**, 681–685 (1969)

Becker, V., Büsscher, V.: Über das Hämangioendotheliom der Leber. Acta hepato-splenol. **8**, 356–379 (1961)

Berk, P.D., Martin, J.F., Young, R.S., Creech, J., Selikoff, I.J., Falf, H., Watanabe, P., Popper, H.: Vinyl-chloride-associated liver disease. Ann. Intern. Med. **84**, 717–731 (1976)

Carr, J.: The fine structure of the mammalian lymphoreticular system. Int. Rev. Cytol. **27**, 283–348 (1970)

Carr, J.: The Kupffer cell. An overview. In: Kupffer cells and other liver sinusoidal cells, E. Wisse and D.L. Knook (Eds.), p. 355. Amsterdam, New York, Oxford: Elsevier/North-Holland Biochemical Press 1977

Edmondson, H.A.: Tumors of the liver and intrahepatic bile ducts. In: Atlas of tumor pathology, Sect. VII, Fasc. 25. Washington, D.C.: Armed Forces Institute of Pathology 1958

Faber, M.: Follow-up of danish Thorotrast cases. Risø Report **294**, 135–145 (1973)

Frenzel, H., Richter, I.-E., Hücker, H.: Rasterelektronenmikroskopische Untersuchungen des RES in der Leber und Milz der Ratte. Verh. Dtsch. Ges. Path. **58**, 551 (1974)

Gedigk, P., Müller, R., Bechtelsheimer, H.: Morphology of liver damage among polyvinyl-chloride production workers. A report on 51 cases. Ann. N.Y. Acad. Sci. **246**, 278–285 (1975)

Gokel, J.M., Liebezeit, E., Eder, M.: Hemangiosarcoma and hepatocellular carcinoma of the liver following vinyl-chloride exposure. Virchows Arch. A Path. Anat. and Histol. **372**, 195–203 (1976)

Grampa, G., Tomasini Degna, A.: Hemangioendothelioma of the liver following intravenous injection of Thorotrast. Acta genet. **8**, 65–78 (1958)

Grampa, G., Cefis, F.: Le cellule di Kupffer dopo iniezione di Thorotrast. Atti Soc. Ital. Pat. 844–847 (1967)

Guimaraes, J.F., Lamerton, L.F., Christensen, W.R.: The late effects of Thorotrast administration. A review and an experimental study. Br. J. Cancer **9**, 253–267 (1955)

Higgins, G.K.: The pathologic anatomy of primary hepatic tumors. Rec. Res. Cancer Res. **26**, 15–37 (1970)

Hofbauer, K., Häring, R.: Intraabdominelle Blutungen bei angioplastischem Sarcom der Leber als Folge einer Isotopen-Spätschädigung (Thorotrast). Med. Welt **13**, 569–572 (1970)

Horta, J. da Silva: Lebersarcom einer Frau, 3 Jahre und 2 Monate nach Thorotrastinjektion. Chirurg **24**, 218–223 (1953)

Horta, J. da Silva, Abbatt, J.D., da Motta, L.C., Roriz, M.L.: Malignancy and other late effects following administration of Thorotrast. Lancet **2**, 201–205 (1965)

Kaick, G. van, Scheer, K.E.: Actual status of the German Thorotrast study. Risø Report **294**, 157–162 (1973)

Leipolz-Angermüller, S.: Tierexperimentelle Untersuchungen zur Carcinogenese von Thorotrast in Organen des RES. Verh. Dtsch. Ges. Path. **60**, 424 (1976)

Motta, P.: A scanning electron microscopic study of the rat liver sinusoid. Cell Tiss. Res. **164**, 371–385 (1975)

Niculescu, P., Rouiller, Ch.: Beziehungen zwischen den Endothelzellen der Lebersinusoide und den von Kupffer'schen Sternzellen. Elektronenmikroskopische Untersuchung. Z. Zellforsch. **76**, 313–338 (1967)

Popper, H., Thomas. L.B.: Alterations of liver and spleen among workers exposed to vinyl chloride. Ann. N.Y. Acad. Sci. **246**, 172–194 (1975)

Popper, H., Thomas L.B., Schaffner, F., Maltoni, C., Selikoff, I.J.: Interaction between sinusoidal cells and hepatocytes in human and experimental angiosarcoma induced by environmental factors. In: Kupffer cells and other liver sinusoidal cells, E. Wisse and D.L. Knook (Eds.), p. 163. Amsterdam, New York, Oxford: Elsevier/North-Holland Biomedical Press 1977

Roth, F.: Arsen-Leber-Tumoren (Hämangioendotheliom). Z. Krebsforsch. **61**, 468–503 (1957)

Strauss, W.: Cytochemical observations on the relationship between lysosomes and phagosomes in kidney and liver by combined staining for acid phosphatase and intravenously injected horseradish peroxydase. J. Cell Biol. **20**, 497–507 (1964)

Tanikawa, K., Ikejiri, N.: Fine structural alterations of the sinusoidal lining cells in various liver diseases. In: Kupffer cells and other liver sinusoidal cells, E. Wisse and D.L. Knook (Eds.). Amsterdam: Elsevier/Nord-Holland Biomedical Press 1977

Tessmer, C.F., Chang, J.P.: Thorotrast localisation by light and electron microscopy. Ann. N.Y. Acad. Sci. **145**, 497–507 (1967)

Thomas, L.B., Popper, H.: Pathology of angiosarcoma of the liver among vinyl chloride-polyvinyl chloride workers. Ann. N.Y. Acad. Sci. **246**, 268–277 (1975)

Vilsfeldt, J., Poulsen, H.: On the histopathology of the liver and liver tumors in Thorium-dioxide patients. Acta path. microbiol. scand. Section A **80**, 97–108 (1972)

Wells A.: cf. Higgins, G.K. The pathologic anatomy of primary hepatic tumors. Rec Res. Cancer Res. **26**, 15–37 (1970)

Wisse, E.: Ultrastructure and function of Kupffer cells and other sinusoidal cells in the liver. In: Kupffer cells and other liver sinusoidal cells, E. Wisse and D.L. Knook (Eds.). Amsterdam: Elsevier/Nord-Holland Biomedical Press 1977

Received August 18, 1978