Virchows Arch. A Path. Anat. and Histol. 364, 179—190 (1974)
© by Springer-Verlag 1974

"Killer"-Lymphocytes in Action?

Light and Electron Microscopical Findings in Orthotopic Liver Homografts

L. Cossel, P.-F. Mahnke, and R. Schwarzer *

Institute of Pathology, Karl-Marx-University, Leipzig

Received March 28, 1974

Summary. Light and electron microscopical findings in orthotopic porcine liver homografts showing small, clear lymphocytes in close contact with circumscribed cell membrane defects, partial lysis, and lytic single cell necroses of liver epithelial cells are described and demonstrated. The interpretation of these results obtained 'in vivo' by the examination of tissue during the host-versus-graft reaction as an equivalent of the cytopathogenetic activity of immunologically activated lymphocytes ("killer"-lymphocytes) causing lysis of target cells, which has been determined by 'in vitro' observation of tissue cultures, is discussed.

Introduction

The results of immunological research have shown that during the reaction of a host organism to an allogeneic (or also xenogeneic) transplant small, specifically sensitized host lymphocytes (also called effector cells, immunocytes, or "killer"-lymphocytes), which are brought in through the circulation of blood tend to invade the foreign tissue and destroy the cells of the transplant by cytolysis after direct contact or close proximity between external cell membranes. This phenomenon is due to a reaction of cell-bound antibodies of lymphocytes with transplant antigens on the cell membranes of transplanted cells. Underlying this pathogenetic concept is the fact that specifically sensitized lymphocytes tend to destroy cells, which has been established by 'in vitro' observation of tissue cultures. The exact mechanism of this cell destruction is uncertain. (For detailed bibliographies see Rosenau 1968, Weiss 1968, Pasternak and Schneeweiss 1973). This process, i.e., the cytopathogenic activity of "killer"-lymphocytes causing lysis of target cells (transplant cells), has not so far been convicingly demonstrated morphologically by 'in vivo' studies in the host organism. To this light and electron microscopical findings are reported and disscussed.

Materials and Methods

The results reported in this paper were obtained from an orthotopically transplanted allogeneic porcine liver.—The tissue was removed by exploratory excision made during laparotomy performed 138 days after transplantation. The operating technique of the transplantation was a modification of the technique described by Starzl (1964) and Starzl *et al.* (1965). For light microscopy tissue blocks of 1 cm^3 were fixed in formalin and absolute alcohol. The following stainings were used: Hematoxylin-eosin, connective-tissue staining by van Gieson's method, Astra blue (pH 4,1), Feulgen's reaction, Gomori's silver staining, and Best's carmine staining.—For electron microscopy liver tissue was separated, within 30 to 90 seconds, into

* Head, Transplantation Group, Clinic of Surgery, Karl-Marx-University.

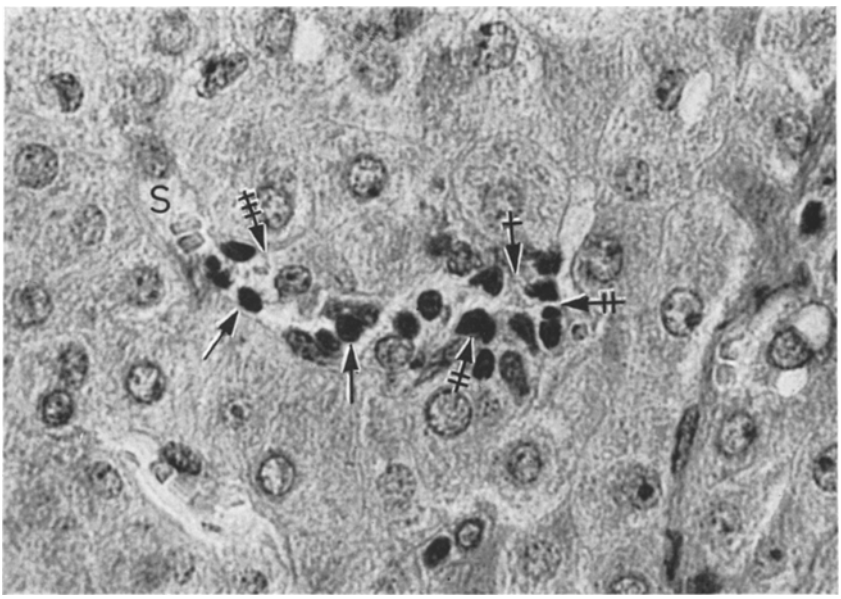

Fig. 1. Sinusoid (*S*) with few lymphocytes (↑), activated endothel cells and macrophages (cp. with Figs. 3—5). To the right: Lytic single cell necrosis (⇞), in place of the lytic hepatocyte lymphocytes and macrophages (⇞) (cp. with Figs. 5 and 6). Peripheral lysis of one hepatocyte (⇞) (cp. with Fig. 5). Orthotopic porcine liver homograft 138 days after transplantation. Van Gieson's staining × 830

1 mm³ pieces on an cooled glass plate and immersed in ice-cooled, 1%, isotonic OsO_4 solution buffered at a pH value of 7,2, the duration of fixation being 2 hours. The material, after having been in contact with tyrode solution for a period of 15 minutes, is dehydrated in an ascending acetone series, 0.5% of phosphotungstic acid and 0.5% of uranyl acetate being added at the 70% acetone level. After this, the material is imbedded in Micropal and then polymerized in an incubator at a temperature of 60° C. An Om U2 type ultramicrotome (C. Reichert, Optische Werke AG, Vienna), was used for the preparation of ultrathin sections. The ultrathin sections were observed with an SEM 3—2 type 100 kv electromagnetic electron microscope (Werk für Fernsehelektronik, Berlin-Oberschöneweide) as well as with a D2 type 50 kv electrostatic electron microscope (VEB Carl Zeiss, Jena).

Results

Small, clear lymphocytes were observed in the lumens of the sinusoids, in the sinusoid wall (Figs. 1, 2b, 3—5), and in the space of Disse. The cell membranes of hepatic epithelial cells located in the neighbourhood of lymphocytes sometimes cannot be detected focally by means of electron microscopy (Figs. 3—5). It is at such points that releases of cytoplasmic constituents into extracellular spaces may be seen (Figs. 3—5). The endothelial sinusoid lining is interrupted in these zones (Figs. 3, 4). And in the immediate neighbourhood there are located macrophages phagocytizing cell debris (Kupffer cells and highly activated endothelial cells, respectively) (Figs. 3, 4), thrombocytes (Fig. 5), and granulocytes with intact cell membranes. Also, small clear lymphocytes were observed in the immediate

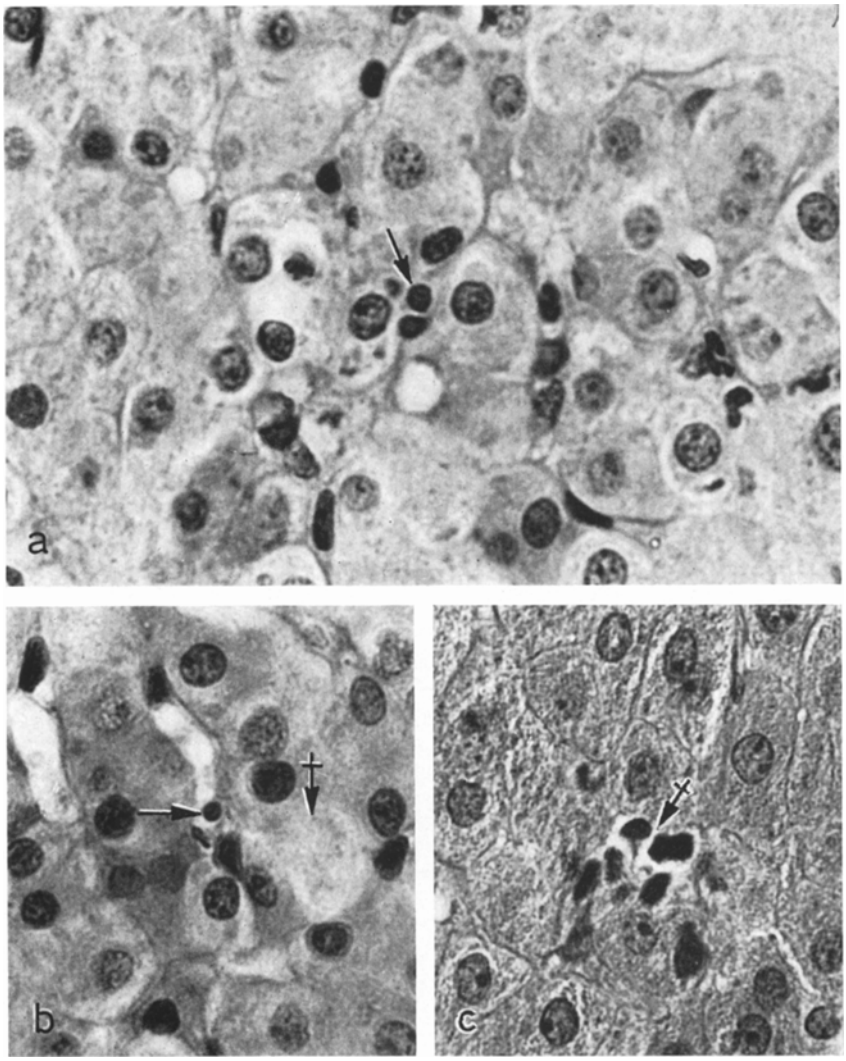

Fig. 2a—c. Relations between lymphocytes, hepatocytes and hepatic single cell necrosis: a) Two lymphocytes in close contact to hepatocytes (↑). b) Small lymphocyte (↑) in a sinusoid (cp. with figures 3—5), nearby a lytic single cell necrosis (↕). c) Lytic single cell necrosis (↕). In place of the lytic hepatocyte lymphocytes and macrophages (cp. with Figs. 5 and 6). Orthotopic porcine liver homograft 138 days after transplantation. Hematoxylin-eosin-staining. × 830

neighbourhood of as well as within either partially or wholly decomposed liver epithelial cells (Figs. 5, 6). Light microscopically, this is the typical finding of lytic single cell necrosis or partial (peripheral) lysis of hepatocytes (Altmann 1955) (Figs. 1, 2b, 2c). The cell membranes of neighbouring liver epithelia are intact (Figs. 5, 6). In all hepatic epithelial cells the endoplasmic

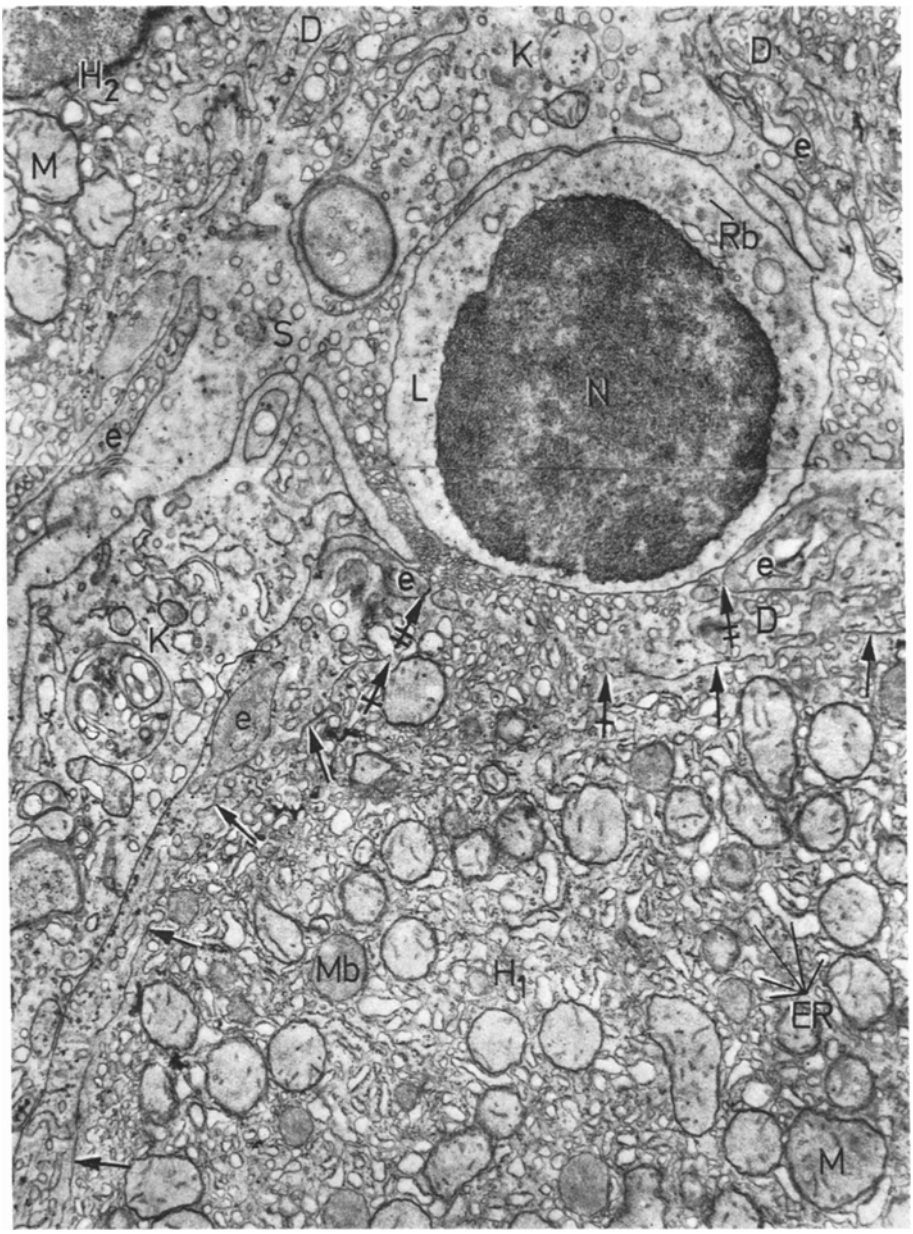

Fig. 3. Small, clear lymphocyte (*L*) in a sinusoid (*S*) in close contact with the endothelial lining (*e*) (cp. with Figs. 1 and 2b). The endothelial sinusoid lining (*e*) is interrupted in this region (between ⫩). The cell membrane (↑) of the neighbouring hepatocyte (H_1) cannot be detected focally at the point nearest to the lymphocytes (between ↕). The release of hepatocyte cytoplasm into the space of Disse (*D*) and the sinusoidal lumen is visible here. *K* Neighbouring macrophages (Kupffer cells or activated endothelial cells, respectively) with phagocytized cell debris in their cytoplasm. Greatly increased and partially dilated smooth and rough surfaced endoplasmic reticulum (*ER*) and some enlarged mitochondria (*M*) with a low-electron-density matrix in the hepatocytes (*H*). *Mb* Microbody. *N* Nucleus of the lymphocyte. The sparse cytoplasm of the lymphocyte contains clear, basic cytoplasmic substance with few ribosomes and a weakly developed smooth endoplasmic reticulum. Orthotopic porcine liver homograft 138 days after transplantation. × 15000

reticulum is considerably increased at the expense of the hyaloplasm. The rough surfaced endoplasmic reticulum seems to be somewhat reduced. The endoplasmic spaces show different degrees of dilatation (Figs. 3—6). The liver cell mitochondria are occasional enlarged and show a moderate electron density of the matrix (Figs. 3—6). Electron miscroscopically, the lymphocytes exhibit roundish to oval, sometimes slightly wavily bounded nuclei with focally differently electron dense granular nucleoplasm, clearly visible perinuclear spaces and a sparse cytoplasm with low electron dense hyaloplasm (Figs. 3—6). The cytoplasm contains only a small amount of smooth tubular endoplasmic reticulum (Figs. 3, 4—6), some relatively large Golgi areas (Fig. 6), and a small number of comparatively large mitochondria (Figs. 5, 6). The hyaloplasm contains a varying number of ribosomes (Figs. 3—6). Ribosomes may sometimes be found to be located at endoplasmic membranes (Fig. 6). The cell membranes of lymphocytes exhibit occasional small and pore-like defects (Figs. 4, 6), which range in size from 200 through 750 Å.

Discussion

The invasion, via blood vessels, of the transplant by lymphocytes and their close contacts with the cells of the transplant has been frequently observed by means of both the light and electron microscope and considered to be a morphological expression of the role played by them in the process of rejection (Medawar, 1944; Kountz *et al.*, 1963; Wiener *et al.*, 1964; Porter *et al.*, 1964; Klion and Schaffner, 1967; Rosenau *et al.*, 1969; Porter, 1969; Hunt, 1967; Roessner *et al.*, 1971; for further bibliographies see Pasternak and Schneeweiss, 1973). Indentation of cytoplasmic processes of contiguous lymphocytes and transplant cells was sometimes observed in the electron microscope. Porter *et al.* (1964), who made electron microscopical studies of the process of rejection of renal homotransplants, also described a decomposition of cell membranes of the immunoblasts and parenchymal cells of the transplant. Such results could not be confirmed by Roessner *et al.* (1971) in their studies of orthotopically transplanted allogeneic dog livers, their results being in agreement with those obtained by Klion and Schaffner (1967) and Rosenau *et al.* (1969). Roessner *et al.* (1971) observed unsharply defined membrane regions of the hepatocytes, pointing out, however, that necroses of parenchymal cells due to close contact with lymphocytes have not been observed by them. In homotransplanted kidneys Kountz *et al.* (1963) did not see any evidence for an immunological attack on renal parenchymal cells. The results obtained for the cell membranes of transplant cells, which have been reported in the publications by Roessner *et al.* (1971), Porter *et al.* (1964) and Kountz *et al.* (1963), do not agree with our results reported here. Hunt (1967), in an electron microscopical study of orthotopic porcine liver homografts, was able to observe large lymphoid cells in the Disse space as well as between hepatic epithelia. He also reported that some lymphocytes seem to lie even within hepatocytes. Porter (1969), in electron microscopical studies of orthotopic canine and human liver homografts, observed lymphoid cells, thrombocytes, and hepatocyte debris in the sinusoids as well as in the space of Disse, which is in agreement with our

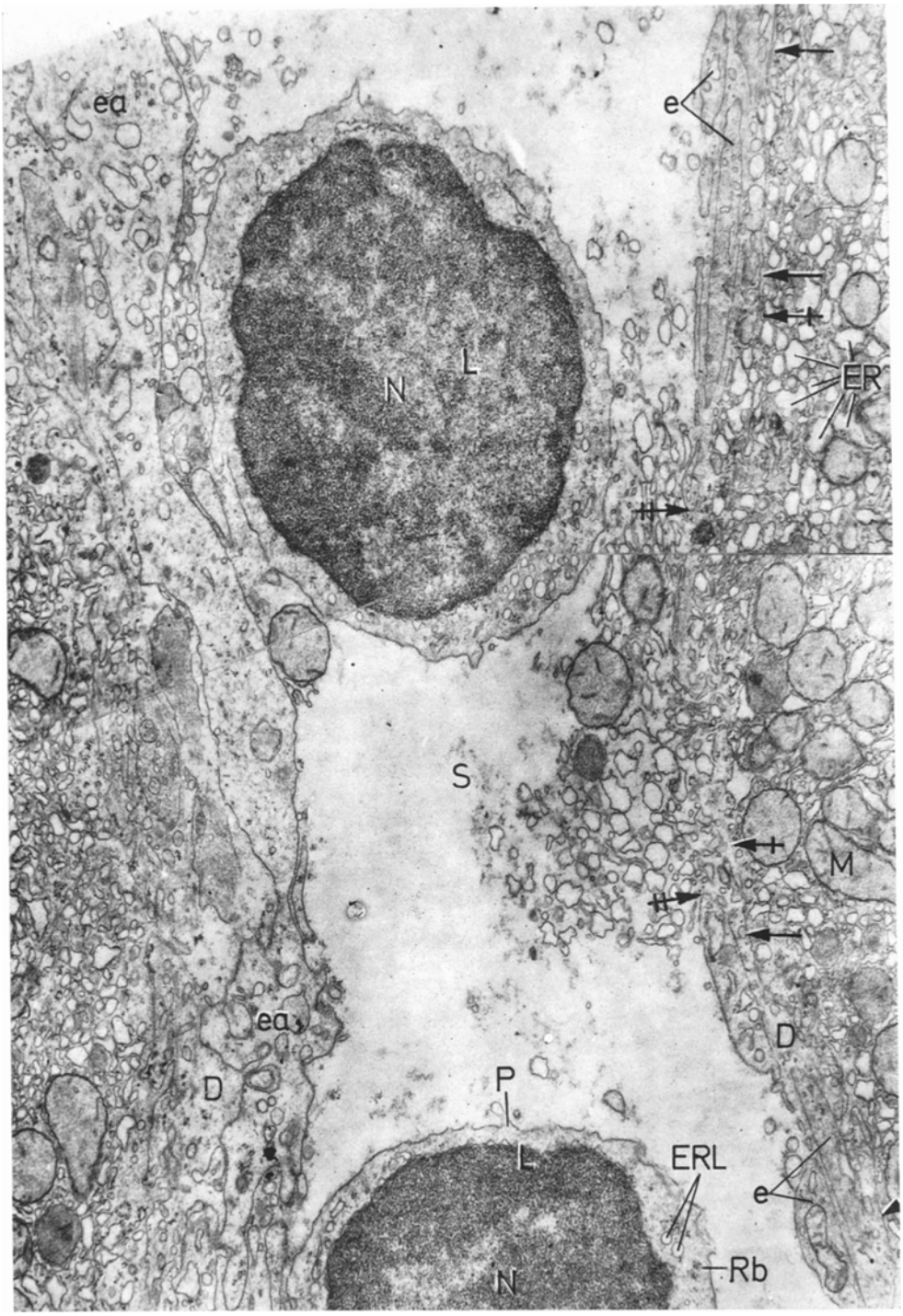

Fig. 4

results. He describes a circumscribed destruction of the endothelial sinusoid lining and observed changes of the endoplasmic reticulum and of the mitochondria of hepatocytes, which are similar to those which were observed by Hunt (1967) and us. The electron micrographs published by Porter show advanced stages of decomposition of hepatic epithelial cells, which are similar to those that may be seen in Figs. 5 and 6 of the present paper. They are described as liver cell debris in the widened space of Disse.

Whereas electron microscopically visible circumscribed defects of the cell membrane of parenchymal cells in transplants, which are described in this paper, have not previously been reported by other investigators, similar conditions of liver cell membranes with releases of components of cytoplasm into extracellular spaces have frequently been observed for liver diseases (such as, for instance, viral hepatitis, chronically relapsing hepatitis, and liver cirrhosis) and in various experiments (effects of toxic substances, hypoxia etc.) (Cossel, 1959, 1966, 1967; Simon and Varonier, 1963; Haenni, 1964; Barka *et al.*, 1964; Rouiller, 1964; Rouiller *et al*, 1965; Ashford and Burdette, 1965; Minio *et al.*, 1965; Lane and Becker, 1966; Boler and Bibighaus, 1967; Meldolesi *et al.*, 1967; Hampton *et al.*, 1968; Porta *et al.*, 1968; Pfeifer and Bannasch, 1968; Pfeifer, 1970, 1973). The general pathological importance of such changes as a potential onset of partial lysis of the periphery and colliquation necrosis (lysis) of hepatic epithelial cells was discussed on the basis of electron microscopical findings obtained in animal experiments and in studies of human liver diseases (Cossel, 1966; Pfeifer, 1970), resuming the thread of conclusions drawn by Altmann (1955) from results of observations made with the light microscope.

It is quite possible for the circumscribed defects in liver cell membranes and the decomposition of hepatocytes to be the results of mechanical preparation artifacts rather than an expression of a vital process, a question that has been discussed by numerous authors. Militating against artificial causes are, for the findings demonstrated in the present paper, the observation by light microscopy of typical lytic single cell necroses (compare Figs. 1, 2b, 2c with Figs. 5, 6) as well as the integrity of neighbouring cells including their cell membranes (Figs. 3—6). The macrophages phagocytizing cell debris (activated Kupffer cells), and thrombocytes in the immediate neighbourhood of cell membrane defects and hepatocytes that are either in the state or in process of colliquation (Figs. 3, 4, 5), which are attracted by the decomposition of cells and the release of tissue thrombokinase, may be considered to be an indication of an intravital process. Pfeifer

Fig. 4. Two lymphocytes (*L*) in a sinusoid (*S*) (cp. with Figs. 1 and 2b). *e* Partially two-layered endothelial sinusoid lining. Some of the endothelial cells are enlarged (activated) (*ea*). The right side of this picture shows an interruption of the endothelial sinusoid lining (*e*) between ⇕. The cell membrane (↑) of the hepatocyte lying here cannot be detected focally (between ↕). Hepatocyte cytoplasm is leaking through this defect in the cell membrane into the Disse space (*D*) and the sinusoid lumen (*S*). Greatly increased and partially dilated endoplasmic reticulum (*ER*) in the hepatocytes. *M* Mitochondria. *N* Lymphocyte nuclei. The sparse cytoplasm of the lymphocytes contains ribosomes (*Rb*) and only a small amount of tubular, smooth, endoplasmic reticulum (*ERL*). *p* Pore-like defect in the cell membrane of a lymphocyte. Orthotopic porcine liver homograft 138 days after transplantation. × 15000

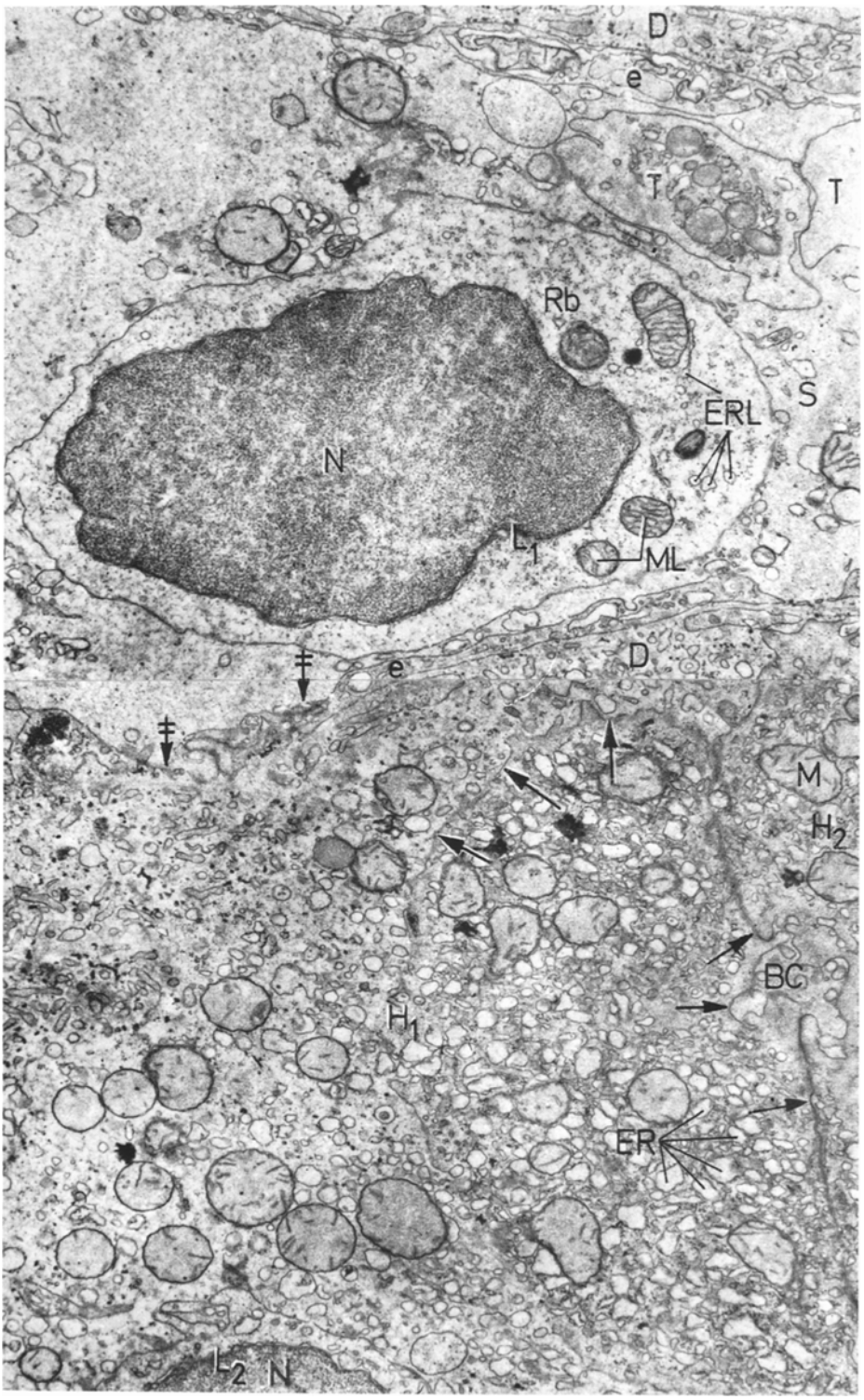

Fig. 5

(1970, see also Pfeifer, 1973) has also pointed out that the defects in liver cell membranes observed by him cannot be satisfactorily explained by the assumption of preparation artifacts, as Kupffer cells were found to react to liberated cytoplasmic components. However, an artificial cause of these findings can not be excluded. But it is discussible to interpret these 'in vivo' findings obtained in the tissue during the host-versus-graft reaction as being light and, especially, electron microscopical equivalents of the lyzing effect of immunologically activated lymphocytes on target cells, which has been observed in tissue cultures. 'In vitro' cinematographic observations display: After a varying period of contact with one or with several lymphoid cells, the target cells suddenly swell and their cell membranes rupture (Rosenau, 1968). The Figs. 3 and 4 might be electron micrographs according to these phases after contact or close approach of the cell membranes of the effector cell (lymphocyte) and target cell (hepatocyte) with decomposition of the target cell membrane at the point of contact and release of cytoplasmic components into extracellular spaces. The Figs. 5 and 6 show advanced stages of this process of decomposition of liver cells up to the point of lytic single cell necrosis. Corresponding electron microscopical 'in vitro' observations are target cell changes consisting of edema, disruption of the plasma membrane, and escape of cytoplasmic components into the surrounding medium described by Able *et al.* (1970). However, these findings are not exemplified by electron micrographs. Weiss (1968), studying the 'in vitro' destruction of target cells in the electron microscope, could not ascertain distinct ruptures of the cell membranes.—The occurence of the demonstrated hepatocyte alterations (Figs. 3, 4) in other liver diseases and under experimental conditions corresponds to the conception that the virtual lysis of target cells (second step) is not necessarily specific (Granger and Williams, 1968; Rosenau, 1968). The specificity is said to be determined by the preceding antibody-antigen reaction on the surfaces of the lymphocytes and target cells (first step) (Rosenau 1968).—It must be considered that the demonstrated findings in hepatocytes might be caused by other factors (e.g. hypoxia, cp. Ashford and Burdette, 1965), and the close proximity of lymphocytes is quite accidental.—It is not at present possible to give an answer to the question as to whether the pore-like defects observed in the cell membranes of lymphocytes and having sizes between 200 and 750 Å (Figs. 4, 6) play a major role in the process of releasing dissolved substances (antibodies or cytotoxic factor? see Granger and Williams, 1968; Weiss, 1968; Rosenau, 1968) or whether they should be considered to be due to tangential cuts of cell surface irregularities.

Fig. 5. Lymphocyte (L_1) in a sinusoid (S) (cp. Figs. 1 and 2b) near the focally not clearly visible (⏚) endothelial sinusoid lining (e). The subjacent hepatic epithelial cell (H_1) is partly dissolved (partial lysis of the cell). A further lymphocyte (L_2) can be seen in the dissolved part thereof (cp. with Figs. 1 and 2c). The unimpaired part is immediately adjacent to an intact hepatic epithelial cell (H_2) which is seen on the right side of this picture. There is a bile canaliculus (BC) in between. The arrows (↑) point at sill unimpaired parts of the external cell membrane of the partly dissolved hepatocyte (H_1). ER Greatly increased and dilated endoplasmic reticulum. M Mitochondria. The sinusoidal lumen contains liver cell debris and thrombocytes (T). D Disse space between endothelial sinusoid lining (e) and hepatocytes (H). N Nuclei, ML Mitochondria, ERL Tubular endoplasmic reticulum, Rb Ribosomes in the clear hyaloplasm of the lymphocytes. Orthotopic porcine liver homograft 138 days after transplantation. × 15000

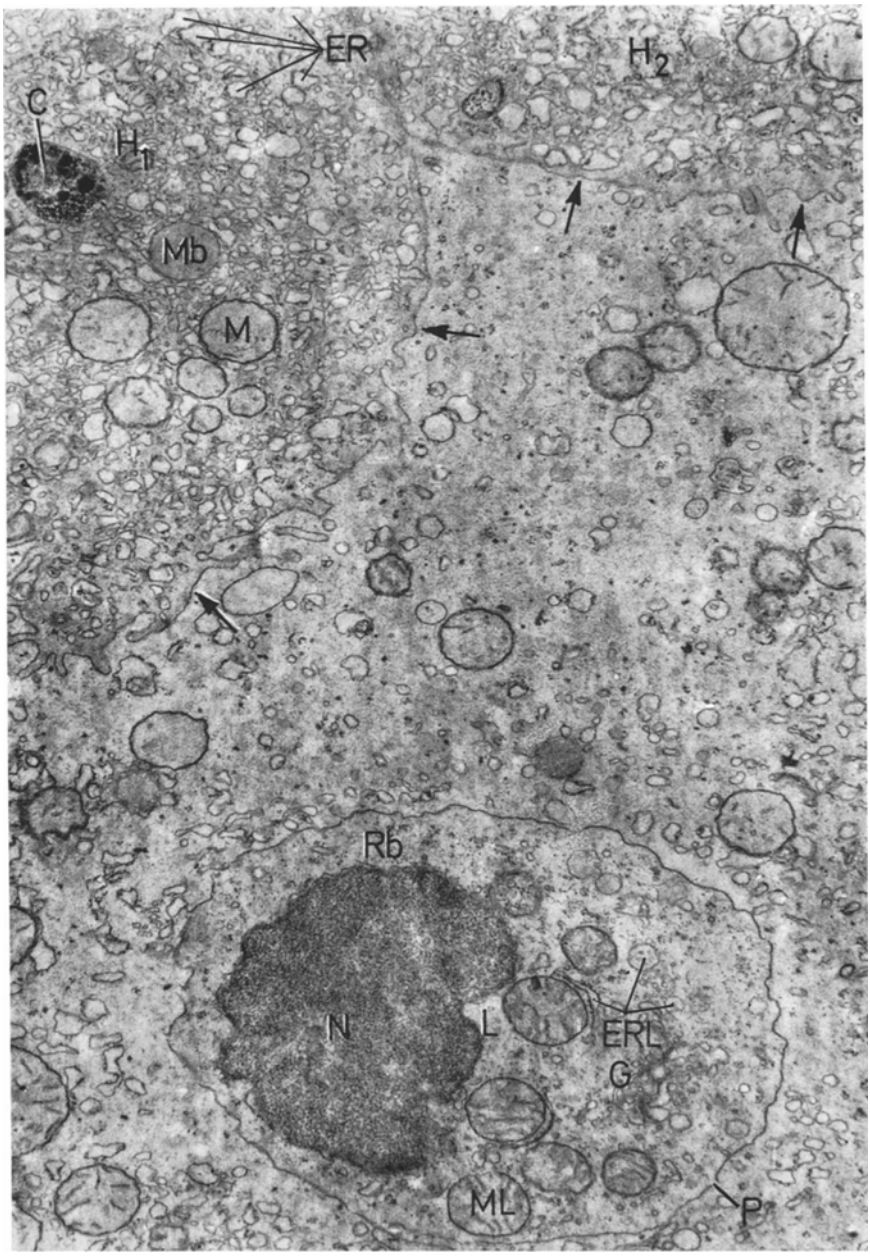

Fig. 6. Small, clear lymphocyte (*L*) within cytoplasmic remains of a dissolved hepatocyte (lytic single cell necrosis) (cp. with Figs. 1 and 2c). The adjacent hepatic epithelia (H_1 and H_2) are unimpaired and have intact cell membranes (↑). *C* Cytosome, *Mb* Microbody, *M* Mitochondria and *ER* Greatly increased endoplasmic reticulum with partially dilated endoplasmic cisternae of liver epithelial cells (*H*). *N* Nucleus, *ML* Mitochondria, *G* Golgi complex, *Rb* Ribosomes, *ERL* Smooth and rough surfaced endoplasmic reticulum of the lymphocyte. *p* Pore-like defect in the cell membrane of the lymphocyte. Orthotopic porcine liver homograft 138 days after transplantation. × 15000

Since immune cellular reactions are known to play an important part in liver diseases accompanied by acute and chronic destruction of parenchymal cells, it is reasonable to assume that lysis (colliquation necrosis) of hepatic epithelial cells (Figs. 1, 2b, 2c, 5, 6) caused by "killer"-lymphocytes is not only a mechanism triggering and supporting the host-versus-graft reaction, but may also, for other forms of liver disease, be the morphological substrate of the factor triggering and supporting the process of disease (self-perpetuation). In this case the well known light microscopical finding of mesenchymal cells (lymphocytes) in the proximity of necrotic or damaged hepatocytes (Figs. 1, 2b, 2c) would not be simply a secondary reaction to hepatocyte injury, but the mesenchymal cells (lymphocytes), in turn, would cause the damage of the hepatocytes (cp. Mackay and Wood, 1961; Burnet, 1961; Popper and Schaffner, 1965). Therefore, it is necessary that in electron microscopical studies of the liver under both pathological and immunological experimental conditions special attention should also in the future be paid to the detection of lymphocytes in connection with circumscribed dissolutions of liver cell membranes and lytic single cell necroses.

References

Able, M. E., Lee, J. C., Rosenau, W.: Lymphocyte-target cell interaction in vitro. Ultrastructural and cinematographic studies. Amer. J. Path. **60**, 421–434 (1970)

Altmann, H. W.: Allgemeine morphologische Pathologie des Cytoplasmas. Die Pathobiosen. In: Handbuch der allgemeinen Pathologie, Bd. II/1, S. 419–612. Berlin-Göttingen-Heidelberg: Springer 1955

Ashford, T. P., Burdette, W. J.: Response of the isolated perfused hepatic parenchyma to hypoxia. Ann. Surg. **162**, 191–207 (1965)

Barka, T., Scheufer, P. J., Schaffner, F., Popper, H.: Structural changes of liver cells in copper intoxication. Arch. Path. **78**, 331–349 (1964)

Boler, R. K., Bibighaus, A. J.: Ultrastructural alterations of dog livers during endotoxin shock. Lab. Invest. **17**, 537–561 (1967)

Burnet, F. M.: The new approach to immunology. New Engl. J. Med. **264**, 24 (1961)

Cossel, L.: Elektronenmikroskopische Untersuchungen an den Lebersinusoiden bei Virushepatitis. Klin. Wschr. **37**, 1263–1278 (1959)

Cossel, L.: Elektronenmiskroskopische Befunde beim intravitalen Untergang von Leberepithelzellen. Beitr. path. Anat. **133**, 156–185 (1966)

Cossel, L.: Electronmicroscopic findings in cirrhosis of the liver. Atti convegni Farmitalia "La cirrosi epatica" Torino: Ed. Minerva Medica 1967

Granger, G. A., Williams, T. W.: Lymphocyte cytotoxicity in vitro: Activation and release of a cytotoxic factor. Nature (Lond.) **218**, 1253–1254 (1968)

Haenni, B.: Les effets de l'intoxication aigue au formiate d'allyl. Etude au microscope electronique. Path. et Microbiol. (Basel) **27**, 974–1002 (1964)

Hampton, J. C., Patterson, R., Rosario, B.: Fine structural changes in livers of dogs in anaphylaxis. Exp. molec. Path. **9**, 258–270 (1968)

Hunt, A. C.: Pathology of liver transplantation in the pig. In: Read, A. E. (ed.), The liver, pp. 337–349. London: Butterworth & Co., Ltd. 1967

Klion, M., Schaffner, F.: Ultrastructural aspects of canine hepatic transplant-rejection. Exp. molec. Path. **6**, 361–369 (1967)

Kountz, S. L., Williams, M. A., Kapros, C., Dempster, W. J.: Mechanism of rejection of homotransplanted kidneys. Nature (Lond.) **199**, 257–260 (1963)

Lane, B. P., Becker, F. F.: Regeneration of the mammalian liver. II. Surface alterations during dedifferentation for cell division. Amer. J. Path. **48**, 183–196 (1966)

Mackay, I. R., Wood, I. J.: Autoimmunity in liver diseases. In: Popper, H., and F. Schaffner (eds.), Progress in liver diseases, Bd. 1, p. 39. New York: Grune & Stratton 1961

Medawar, P. B.: The behaviour and fate of skin homografts in rabbits. J. Anat. (Lond.) **78**, 176–199 (1944)

Meldolesi, J., Pelosi, G., Brunelli, A., Genovese, E.: Electron microscopic studies on the effects of amanitin in mice: Liver and heart lesions. Virchows Arch. path. Anat. **342**, 221–235 (1967)

Minio, F., Alberti, F., Gardiol, A., Magnenant, P., Torsoli, A.: L'ultrastructure du foie humain lors d'ictére à bilirubine directe. Z. Zellforsch. **66**, 496–503 (1965)

Pasternak, G., Schneeweiss, U.: Transplantations- und Tumorimmunologie. Jena: VEB Gustav Fischer 1973

Pfeifer, U.: Über Endocytose in Kupfferschen Sternzellen nach Parenchymschädigung durch $^3/_4$-Teilhepatektomie. Virchows Arch. Abt. B **6**, 263–280 (1970)

Pfeifer, U.: Cellular autophagy and cell atrophy in the rat liver during long-term starvation. Virchows Arch. Abt. B. **12**, 195–211 (1973)

Pfeifer, U., Bannasch, P.: Zum Problem der „hyalinen Eiweißtropfen" im Cytoplasma der Leberparenchymzellen. Licht- und elektronenmikroskopische Untersuchungen nach $^3/_4$-Hepatektomie. Virchows Arch. Abt. B. **1**, 365–388 (1968)

Popper, H., Schaffner, F.: The problem of chronicity in liver disease. In: Progress in liver diseases, eds. H. Popper and F. Schaffner, vol. 2, p. 519–538. New York, London: Grune & Stratton 1965

Porta, E. A., Iglesia, F. A. de la, Hartroft, W. S.: Studies on dietary hepatic necrosis. Lab. Invest. **18**, 283–297 (1968)

Porter, K. A.: Pathology of the orthotopic homograft and heterograft. In: Starzl, T. E. and Putmann, C. W. (eds.), Experience in hepatic transplantation, pp. 422–471. Philadelphia-London-Toronto: W. B. Saunders Comp. 1969

Porter, K. A., Joseph, N. H., Kendall, J. M., Stollinky, C., Hoehn, R. J., Calne, R. Y.: The role of lymphocytes in the rejection of canine renal homotransplants. Lab. Invest. **13**, 1080–1091 (1964)

Roessner, A., Lie, T. S., Schultz, D., Bassewitz, D. B. v., Themann, H.: Zur Feinstruktur der orthotop transplantierten, allogenen Hundeleber. Virchows Arch. Abt. B. **9**, 354–370 (1971)

Rosenau, W.: Target cell destruction. Fed. Proc. **27**, 34–38 (1968)

Rosenau, W., Lee, J. C., Najarian, J. S.: A light-, fluorescence- and electron-microscopic study of functioning human transplants. Surg. Gynec. Obstet. **128**, 62–76 (1969)

Rouiller, Ch.: The liver. Morphology, biochemistry, physiology, vol. 2. New York-London: Acad. Press 1964

Rouiller, Ch., Colombey, N., Haenni, B., Perrelet, A., Torrente, A. de: Les modifications de la parois des capillaires sinusoides du foie dans les intoxications aigues expérimentales. Rev. int. Hépat. **15**, 437–453 (1965)

Simon, G., Varonier, H. S.: Etude au microscope électronique du foie de deux cas d'ictére non hémolytique congénital de type Gilbert. J. suisse méd. **1963**, 459–464

Starzl, T. E.: Experimental and clinical homotransplantation of the liver. Ann. N. Y. Acad. Sci. **120**, 739 (1964)

Starzl, T. E., Marchioro, J. L., Porter, K. A.: Experimental clinical observations after homotransplantation of the whole liver. Rev. int. Hepat. **15**, 1447 (1965)

Weiss, L.: Interactions of sensitized lymphoid cells and homologous target cells in tissue culture and in grafts. An electron microscopic and immunofluorescence study. J. Immunol. **101**, 1346–1362 (1968)

Wiener, J., Spiro, D., Russell, P. S.: An electron microscopic study of the homograft reaction. Amer. J. Path. **44**, 319–347 (1964)

Prof. Dr. Lothar Cossel
Pathologisches Institut
der Karl-Marx-Universität
DDR-701 Leipzig
Liebigstr. 26
German Democratic Republic